

# COMPUTER SYSTEMS AND METHODS FOR CONSTRUCTING BIOLOGICAL CLASSIFIERS AND USES THEREOF

This application is entitled to and claims priority benefit under 35 U.S.C. Section 119(e) to U.S. provisional application Number 60/581,312, filed June 19, 2004, U.S. provisional application Number 60/581,977, filed June 21, 2004, U.S. provisional application Number 60/643,475, filed January 12, 2005, and U.S. provisional application Number 60/663,722, filed March 22, 2005, each of which is incorporated herein by reference in its entirety.

## 1. FIELD OF THE INVENTION

The field of this invention relates to computer systems and methods to identify classifiers using data obtained from blood. The invention further encompasses the use of the classifiers and combinations of molecular markers identified by the classifiers in a wide variety of applications including: diagnosis; prognosis; prediction of disease, stage of disease or disease risk; monitoring disease progression and/or regression; monitoring disease reoccurrence and identifying risk of disease reoccurrence; determining and/or predicting response to treatment and/or treatment outcomes; monitoring and/or predicting treatment compliance or non compliance and the like.

<u>Table</u>	<u>DESCRIPTION</u>	<u>SIZE</u>	<u>Date Recorded</u>	<u>Text File Name</u>
1A	Sequence Related Table regarding Comorbid Hypertension	96KB	June 17, 2005	TABLE1A.TXT
1B	Sequence Related Table regarding Comorbid Obesity	102KB	June 17, 2005	TABLE1B.TXT
1C	Sequence Related Table regarding Comorbid Allergies	49KB	June 17, 2005	TABLE1C.TXT
1D	Sequence Related Table regarding Comorbid Systemic Steroids	59KB	June 17, 2005	TABLE1D.TXT
1E	Sequence Related Table regarding Hypertension (Chondro)	204KB	June 17, 2005	TABLE1E.TXT
1F	Sequence Related Table regarding Obesity (Chondro)	251KB	June 17, 2005	TABLE1F.TXT
1G	Sequence Related Table regarding CoMorbid Hypertension Only	57KB	June 17, 2005	TABLE1G.TXT
1H	Sequence Related Table regarding Hypertension OA Shared	23KB	June 17, 2005	TABLE1H.TXT
1I	Sequence Related Table regarding Comorbid Obesity Only	60KB	June 17, 2005	TABLE1I.TXT

1J	Sequence Related Table regarding Obesity OA Shared	18KB	June 17, 2005	TABLE1J.TXT
1K	Sequence Related Table regarding Comorbid Allergy Only	28KB	June 17, 2005	TABLE1K.TXT
1L	Sequence Related Table regarding Allergy OA Shared	19KB	June 17, 2005	TABLE1L.TXT
1M	Sequence Related Table regarding Comorbid Steroid Shared	40KB	June 17, 2005	TABLE1M.TXT
1N	Sequence Related Table regarding Steroid OA Shared	23KB	June 17, 2005	TABLE1N.TXT
1O	Sequence Related Table regarding Differentiating Systemic Steroids (	49KB	June 17, 2005	TABLE1O.TXT
1P	Sequence Related Table regarding Diabetes	118KB	June 17, 2005	TABLE1P.TXT
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1R	Sequence Related Table regarding Lung Disease	102KB	June 17, 2005	TABLE1R.TXT
1S	Sequence Related Table regarding Bladder Cancer	830KB	June 17, 2005	TABLE1S.TXT
1T	Sequence Related Table regarding Bladder Cancer Staging	483KB	June 17, 2005	TABLE1T.TXT
1U	Sequence Related Table regarding Coronary Artery Disease	657KB	June 17, 2005	TABLE1U.TXT
1V	Sequence Related Table regarding Rheumatoid Arthritis	380KB	June 17, 2005	TABLE1V.TXT
1W	Sequence Related Table regarding Rheumatoid Arthritis	183KB	June 17, 2005	TABLE1W.TXT
1X	Sequence Related Table regarding Depression	165KB	June 17, 2005	TABLE1X.TXT
1Y	Sequence Related Table regarding OAStaging	32KB	June 17, 2005	TABLE1Y.TXT
1Z	Sequence Related Table regarding Liver Cancer	19KB	June 17, 2005	TABLE1Z.TXT
1Zb	Sequence Related Table regarding Liver Cancer	430KB	June 17, 2005	TABLE1Z.TXT
1AA	Sequence Related Table regarding Schizophrenia	592KB	June 17, 2005	TABLE1AA.TXT
1AB	Sequence Related Table regarding Chagas Disease	142KB	June 17, 2005	TABLE1AB.TXT
1AC	Sequence Related Table regarding Asthma (Chondro)	64KB	June 17, 2005	TABLE1AC.TXT
1AD	Sequence Related Table regarding Asthma (Affy)	57KB	June 17, 2005	TABLE1AD.TXT



1AE	Sequence Related Table regarding Lung Cancer	118KB	June 17, 2005	TABLE 1AE.TXT
1AG	Sequence Related Table regarding Hypertension (Affymetrix)	157KB	June 17, 2005	TABLE1AG.TXT
1AH	Sequence Related Table regarding Obesity (Affymetrix)	203KB	June 17, 2005	TABLE1AH.TXT
1AI	Sequence Related Table regarding Ankylosing Spondylitis (Affy)	267KB	June 17, 2005	TABLE1AI.TXT
2	Sequence Related Table regarding OA Only Subtraction	19KB	June 17, 2005	TABLE2.TXT
3A	Sequence Related Table regarding Schizophrenia v. MDS	228KB	June 17, 2005	TABLE3A.TXT
3B	Sequence Related Table regarding Hepatitis v. Liver Cancer	347KB	June 17, 2005	TABLE3B.TXT
3C	Sequence Related Table regarding Bladder Cancer v. Kidney Cancer	470KB	June 17, 2005	TABLE3C.TXT
3D	Sequence Related Table regarding Bladder Cancer v. Testicular Cancer	556KB	June 17, 2005	TABLE3D.TXT
3E	Sequence Related Table regarding Testicular Cancer v. Kidney Cancer	588KB	June 17, 2005	TABLE3E.TXT
3F	Sequence Related Table regarding Liver Cancer v. Stomach Cancer	84KB	June 17, 2005	TABLE3F.TXT
3G	Sequence Related Table regarding Liver Cancer v. Colon Cancer	149KB	June 17, 2005	TABLE3G.TXT
3H	Sequence Related Table regarding Stomach Cancer v. Colon Cancer	166KB	June 17, 2005	TABLE3H.TXT
3I	Sequence Related Table regarding OA v. RA	214KB	June 17, 2005	TABLE3I.TXT
3K	Sequence Related Table regarding Chagas Disease v.Heart Failure	16KB	June 17, 2005	TABLE3K.TXT
3L	Sequence Related Table regarding Chagas Disease v. CAD	19KB	June 17, 2005	TABLE3L.TXT
3N	Sequence Related Table regarding CAD v. Heart Failure	13KB	June 17, 2005	TABLE3N.TXT
3P	Sequence Related Table regarding Asymptomatic Chagas v. Symptomatic	68KB	June 17, 2005	TABLE3P.TXT

	Chagas			
3Q	Sequence Related Table regarding Alzheimers' v. Schizophrenia	56KB	June 17, 2005	TABLE3Q.TXT
3R	Sequence Related Table regarding Alzheimers' v. Manic Depression	51KB	June 17, 2005	TABLE3R.TXT
4A	Sequence Related Table regarding OA v. Control (ChondroChip)	538KB	June 17, 2005	TABLE4A.TXT
4B	Sequence Related Table regarding OA v. Control (Affy)	550KB	June 17, 2005	TABLE4B.TXT
4C	Sequence Related Table regarding OA mild v. Control (ChondroChip)	321KB	June 17, 2005	TABLE4C.TXT
4D	Sequence Related Table regarding OA mild v. Control (Affy)	587KB	June 17, 2005	TABLE 4D.TXT
4E	Sequence Related Table regarding OA moderate v. Control (ChondroChip)	198KB	June 17, 2005	TABLE4E.TXT
4F	Sequence Related Table regarding OA moderate v. Control (Affy)	576KB	June 17, 2005	TABLE4F.TXT
4G	Sequence Related Table regarding OA marked v. Control (ChondroChip)	203KB	June 17, 2005	TABLE4G.TXT
4H	Sequence Related Table regarding OA marked v. Control (Affy)	679KB	June 17, 2005	TABLE4H.TXT
4I	Sequence Related Table regarding OA severe v. Control (ChondroChip)	291KB	June 17, 2005	TABLE4I.TXT
4J	Sequence Related Table regarding OA severe v. Control (Affy)	607KB	June 17, 2005	TABLE4J.TXT
4K	Sequence Related Table regarding OA mild v. moderate (ChondroChip)	113KB	June 17, 2005	TABLE4K.TXT
4L	Sequence Related Table regarding OA mild v. moderate (Affy)	488KB	June 17, 2005	TABLE4L.TXT
4M	Sequence Related Table regarding OA mild v. marked (ChondroChip)	93KB	June 17, 2005	TABLE4M.TXT
4N	Sequence Related Table regarding OA mild v. marked (Affy)	373KB	June 17, 2005	TABLE4N.TXT
4O	Sequence Related Table regarding OA mild v. severe	177KB	June 17, 2005	TABLE4O.TXT

	(ChondroChip)			
4P	Sequence Related Table regarding OA mild v. severe (Affy)	687KB	June 17, 2005	TABLE4P.TXT
4Q	Sequence Related Table regarding OA moderate v. marked (ChondroChip)	103KB	June 17, 2005	TABLE4Q.TXT
4R	Sequence Related Table regarding OA moderate v. marked (Affy)	450KB	June 17, 2005	TABLE4R.TXT
4S	Sequence Related Table regarding OA moderate v. severe (ChondroChip)	79KB	June 17, 2005	TABLE4S.TXT
4T	Sequence Related Table regarding OA moderate v. severe (Affy)	627KB	June 17, 2005	TABLE4T.TXT
4U	Sequence Related Table regarding OA marked v. severe (ChondroChip)	66KB	June 17, 2005	TABLE4U.TXT
4V	Sequence Related Table regarding OA marked v. severe (Affy)	758KB	June 17, 2005	TABLE4V.TXT
5A	Sequence Related Table regarding Psoriasis v. Control	80KB	June 17, 2005	TABLE5A.TXT
5B	Sequence Related Table regarding Thyroid Disorder v. Control	373KB	June 17, 2005	TABLE5B.TXT
5C	Sequence Related Table regarding Irritable Bowel Syndrome v. Control	87KB	June 17, 2005	TABLE5C.TXT
5D	Sequence Related Table regarding Osteoporosis v. Control	79KB	June 17, 2005	TABLE5D.TXT
5E	Sequence Related Table regarding Migraine Headaches v. Control	231KB	June 17, 2005	TABLE5E.TXT
5F	Sequence Related Table regarding Eczema v. Control	56KB	June 17, 2005	TABLE5F.TXT
5G	Sequence Related Table regarding NASH v. Control	349KB	June 17, 2005	TABLE5G.TXT
5H	Sequence Related Table regarding Alzheimers' v. Control	268KB	June 17, 2005	TABLE5H.TXT
5I	Sequence Related Table regarding Manic Depression v. Control	298KB	June 17, 2005	TABLE5I.TXT
5J	Sequence Related Table regarding Crohns' Colitis v. Control	45KB	June 17, 2005	TABLE5J.TXT
5K	Sequence Related Table regarding Chronic Cholecystitis	53KB	June 17, 2005	TABLE5K.TXT

	v. Control			
5L	Sequence Related Table regarding Heart Failure v. Control	160KB	June 17, 2005	TABLE5L.TXT
5M	Sequence Related Table regarding Cervical Cancer v. Control	304KB	June 17, 2005	TABLE5M.TXT
5N	Sequence Related Table regarding Stomach Cancer v. Control	185KB	June 17, 2005	TABLE5N.TXT
5O	Sequence Related Table regarding Kidney Cancer v. Control	404KB	June 17, 2005	TABLE5O.TXT
5P	Sequence Related Table regarding Testicular Cancer v. Control	486KB	June 17, 2005	TABLE5P.TXT
5Q	Sequence Related Table regarding Colon Cancer v. Control	380KB	June 17, 2005	TABLE5Q.TXT
5R	Sequence Related Table regarding Hepatitis B v. Control	140KB	June 17, 2005	TABLE5R.TXT
5S	Sequence Related Table regarding Pancreatic Cancer v. Control	177KB	June 17, 2005	TABLE5S.TXT
5T	Sequence Related Table regarding Asymptomatic Chagas v. Control	63KB	June 17, 2005	TABLE5T.TXT
5U	Sequence Related Table regarding Symptomatic Chagas v. Control	77KB	June 17, 2005	TABLE5U.TXT
5V	Sequence Related Table regarding Bladder Cancer v. Control	383KB	June 17, 2005	TABLE5V.TXT
6A	Sequence Related Table regarding Cancer (all types) v. Control	163KB	June 17, 2005	TABLE6A.TXT
6B	Sequence Related Table regarding Cardiovascular Disease v. Control	73KB	June 17, 2005	TABLE6B.TXT
6C	Sequence Related Table regarding Neurological Diseases v. Control	337KB	June 17, 2005	TABLE6C.TXT
7A	Sequence Related Table regarding Celebrex® v. all Cox inhibitors except Celebrex	55KB	June 17, 2005	TABLE7A.TXT
7B	Sequence Related Table regarding Celebrex® v. Control	57KB	June 17, 2005	TABLE7B.TXT
7C	Sequence Related Table	53KB	June 17,	TABLE7C.TXT

	regarding Vioxx® v. Control		2005	
7D	Sequence Related Table regarding Vioxx® v. All Cox Inhibitors except Vioxx®	49KB	June 17, 2005	TABLE7D.TXT
7E	Sequence Related Table regarding NSAIDS v. Control	72KB	June 17, 2005	TABLE7E.TXT
7F	Sequence Related Table regarding Cortisone v. Control	208KB	June 17, 2005	TABLE7F.TXT
7G	Sequence Related Table regarding Visco Supplement v. Control	316KB	June 17, 2005	TABLE7G.TXT
7H	Sequence Related Table regarding Lipitor® v. Control	131KB	June 17, 2005	TABLE7H.TXT
7I	Sequence Related Table regarding Smoker v. Non- Smoker	23KB	June 17, 2005	TABLE7I.TXT

## 2. BACKGROUND OF THE INVENTION

The prior art is deficient in simple, non-invasive and effective methods of identifying molecular markers and the use of said molecular markers for purposes of: diagnosis; prognosis; prediction of disease, stage of disease or disease risk; monitor  
5 disease progression and/or regression; monitor disease reoccurrence and identifying risk of disease reoccurrence or the like. The prior art is also deficient in simple non-invasive methods of identifying molecular markers and use of said molecular markers to determine and/or predict response to treatment and/or treatment outcomes, monitor and/or predict treatment compliance or non-compliance, etc. Although progress has been made in  
10 identifying molecular markers by detecting the products of putative molecular markers using expression arrays in a variety of diagnostic areas and therapeutic areas, such progress has been primarily limited to studying non-blood tissue samples, such as primary tumors, that are difficult to obtain and thus have limited potential as a diagnostic. What is even more unsatisfactory is that retrieval of such tissue samples often requires invasive  
15 medical procedures such as surgery. Prediction of response to treatment is also a significant problem. It is well understood that, for many currently recognized treatments, only a small percentage of the population (for example approximately 20-30%) will respond positively. Amongst the remainder of the population, there are those who do not improve, and others who display a negative or toxic response to the treatment. As a result  
20 of these detrimental effects to some, many effective treatments do not get to market. The prior art is thus deficient in simple, non-invasive methods to analyze and predict treatment and response to treatment.

Such drawbacks have made identification of molecular markers unsatisfactorily difficult. See, for example, Alon *et al.*, 1999, Proc. Natl. Acad. Sci. USA 96, pp. 6745-6750; Schummer *et al.*, 1999, Gene 238, pp. 375-385; and van't Veer, 2002, Nature 415, pp. 530-536.

5 Even where progress has been made in identifying molecular markers by monitoring molecular marker products using expression arrays – whether in blood or using tissue – the techniques utilized merely identify large number of molecular markers two or more of which may be required so as to permit categorizing an unknown sample for diagnosis. It is not clear, however, which of these molecular markers are most useful to  
10 accurately diagnose an unknown sample. In addition, techniques currently available in the art are not sufficiently robust (ie high levels of reproducibility) in accordance with scientific and regulatory standards so as to be used reliably to diagnose a test individual. Thus what is required in the art is a means to select smaller subsets of useful molecular markers which when used in combination permit the accurate and reproducible diagnosis  
15 of an unknown sample for a particular trait of interest. Further what is required in the art is a means of translating the molecular marker data from these selected combinations so as to convert these into a diagnosis.

Discussion or citation of a reference herein will not be construed as an admission that such reference is prior art to the present invention.

### 20 3. SUMMARY OF THE INVENTION

Thus what is needed in the art is a method to identify useful combinations of molecular markers and a means of using said combinations of molecular markers (or more accurately measurement of the products of said molecular markers) so as to permit diagnosis of a test sample. Embodiments of the present invention address many of the  
25 shortcomings and drawbacks found in the prior art by the novel approach of using molecular marker measurement data from blood and methods of processing such data to screen the large numbers of candidate molecular markers in blood so as to identify useful combinations of these molecular markers. Embodiments of the present invention involve the construction of classifiers and use of these classifiers. In addition, embodiments of the  
30 invention involve the use of the molecular markers identified by these classifiers to diagnose or otherwise determine whether a test subject has a specific trait of interest. Blood offers a surprisingly informative alternative to tissues as a source of information. Blood includes numerous cell types including monocytes, leukocytes, lymphocytes, erythrocytes, platelets, as well as possibly many other cell types. The turnover of cells in

the human circulatory system is rapid. As a consequence of continuous interactions between the blood and the body, it has been hypothesized that the changes that occur within the cells or tissues of the body will trigger specific changes in gene expression within blood. See, for example, United States patent application serial No. 10/601,518, filed June 20, 2003, United States patent application serial No. 10/802,875, filed March 12, 2004, United States patent application serial No. 10/809,675, filed March 25, 2004, United States patent application serial No. 10/268,730, filed October 9, 2002, United States patent application serial No. 09/477,148, filed January 4, 2000, and United States patent application serial No. 60/115,125, filed Jan. 6, 1999, which are hereby incorporated herein by reference in their entirety. Thus, blood has the potential to provide a powerful indicator of what is happening in the human body at any given time, but provides unique challenges to harness this vast amount of potential information available. Embodiments of the current invention help address this challenge.

#### 4. BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 illustrates a computer system for determining and selecting useful biological classifiers.

Fig. 2 illustrates a method for deriving biological classifiers in accordance with an embodiment of the present invention.

Fig. 3 is a flowchart of a method of applying the classifiers to a patient.

Fig. 4 illustrates a data structure for storing high throughput information for a plurality of molecular markers in accordance with one embodiment of the present invention.

Fig. 5 illustrates a data structure for storing a plurality of classifiers in accordance with one embodiment of the present invention.

Fig. 6 illustrates a patient database for storing data for molecular markers for a plurality of patients in accordance with an embodiment of the present invention.

Fig. 7 illustrates a Receiver Operating Characteristic (ROC) curve that is used to assess the discriminating ability of a molecular marker or a classifier in accordance with one embodiment of the present invention.

Fig. 8 illustrates ROC curves corresponding to two candidate classifiers for osteoarthritis computed in accordance with one embodiment of the present invention.

#### **Description of Tables:**

**Table 1** as a group of tables identifies the molecular markers that are differentially expressed in blood samples from patients with a disease or patients who are co-morbid as

compared to blood samples from healthy patients or patients without said disease, or with only one of said co-morbid diseases and also shows the sequences of selected products of the identified molecular markers. Molecular marker data from the molecular markers listed in each table or a subset of these molecular markers can be used can be used in steps 214-  
5 218 as outlined in Figure 2B so as to identify classifiers and the combinations of molecular markers which form the classifiers useful in diagnosis.

**Table 1A** identifies the molecular markers which are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has both osteoarthritis and hypertension as compared with a  
10 second trait subgroup wherein each member of the second trait subgroup has neither osteoarthritis nor hypertension using the ChondroChip™ platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 1B** shows the identity of those molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup  
15 where each member of the subgroup has both osteoarthritis and obesity as compared with a second trait subgroup wherein each member of the second trait subgroup has neither osteoarthritis nor obesity using the ChondroChip™ platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 1C** shows the molecular markers that are differentially expressed in blood  
20 samples from a training population comprised of a first trait subgroup where each member of the subgroup has both osteoarthritis and allergies as compared with a second trait subgroup wherein each member of the second trait subgroup has neither osteoarthritis nor allergies using the ChondroChip™ platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 1D** shows the molecular markers that are differentially expressed in blood  
25 samples from a training population comprised of a first trait subgroup where each member of the subgroup has both osteoarthritis and subject to systemic steroids as compared with normal patients using the ChondroChip™ platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 1E** shows the molecular markers that are differentially expressed in blood  
30 samples from a training population comprised of a first trait subgroup where each member of the subgroup has hypertension as compared to a second trait subgroup wherein each member of the second trait subgroup did not have hypertension using the ChondroChip™



platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 1F** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member  
5 of the subgroup has obesity as compared to a second trait subgroup wherein each member of the second trait subgroup did not have obesity using the ChondroChip™ platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 1G** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member  
10 of the subgroup has hypertension and OA when compared with a second trait subgroup wherein each member of the second trait subgroup have OA only wherein molecular markers identified in Table 1A have been removed so as to identify molecular markers which are unique to hypertension. The table also shows the sequences of selected products of the identified molecular markers.

**Table 1H** shows the molecular markers which were identified in Table 1A which  
15 are shared with those molecular markers differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has both hypertension and OA when compared with a second trait subgroup wherein each member of the second trait subgroup have OA only. The table also shows the sequences of  
20 selected products of the identified molecular markers.

**Table 1I** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member  
of the subgroup has both obesity and have OA when compared with a second trait subgroup wherein each member of the second trait subgroup have OA only and wherein  
25 molecular markers identified in Table 1B have been removed so as to identify molecular markers which are unique to obesity. The table also shows the sequences of selected products of the identified molecular markers.

**Table 1J** shows the molecular markers identified in Table 1B which are shared  
with those molecular markers differentially expressed in blood samples from patients who  
30 are obese and have OA when compared with patients who have OA. The table also shows the sequences of selected products of the identified molecular markers.

**Table 1K** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member  
of the subgroup has both allergies and OA when compared with a second trait subgroup

wherein each member of the second trait subgroup have OA only wherein molecular markers identified in Table 1C have been removed so as to identify molecular markers which are unique to allergies. The table also shows the sequences of selected products of the identified molecular markers.

5           **Table 1L** shows the identify of those molecular markers identified in Table 3C which are shared with those molecular markers differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has both allergies and OA when compared with a second trait subgroup wherein each member of the second trait subgroup having OA only. The table also shows the  
10 sequences of selected products of the identified molecular markers.

**Table 1M** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup is taking systemic steroids and has OA when compared with a second trait subgroup wherein each member of the second trait subgroup have OA only wherein  
15 molecular markers identified in Table 1D have been removed so as to identify molecular markers which are unique to patients on systemic steroids. The table also shows the sequences of selected products of the identified molecular markers.

**Table 1N** shows the identify of those molecular markers identified in Table 1D which are shared with those molecular markers differentially expressed in blood samples  
20 from a training population comprised of a first trait subgroup where each member of the subgroup who are on systemic steroids and have OA when compared with a second trait subgroup wherein each member of the second trait subgroup have OA only. The table also shows the sequences of selected products of the identified molecular markers.

**Table 1O** shows the molecular markers that are differentially expressed in blood  
25 from a training population comprised of a first trait subgroup where each member of the subgroup are either taking birth control, on prednisone or on hormone replacement therapy and presenting with OA using the ChondroChip™ platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 1P** shows the molecular markers that are differentially expressed in blood  
30 samples from a training population comprised of a first trait subgroup where each member of the subgroup has both type II diabetes as compared to a second trait subgroup wherein each member of the second trait subgroup does not have type II diabetes using the ChondroChip™ platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 1Q** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has Hyperlipidemia as compared to a second trait subgroup wherein each member of the second trait subgroup does not have Hyperlipidemia using the

5 ChondroChip™ platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 1R** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has lung disease as compared to a second trait subgroup wherein each  
10 member of the second trait subgroup does not have lung disease using the ChondroChip™ platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 1S** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member  
15 of the subgroup has bladder cancer as compared to a second trait subgroup wherein each member of the second trait subgroup does not have bladder cancer using the ChondroChip™ platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 1T** shows the molecular markers that are differentially expressed in blood  
20 samples from a training population comprised of a first trait subgroup where each member of the subgroup has early stage bladder cancer, late stage bladder cancer with a second trait subgroup wherein each member of the second trait subgroup does not have bladder cancer using the ChondroChip™ platform. The table also shows the sequences of selected products of the identified molecular markers.

25 **Table 1U** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has coronary artery disease (CAD) as compared to a second trait subgroup wherein each member of the second trait subgroup does not have not having CAD using the ChondroChip™ platform. The table also shows the sequences of selected products of  
30 the identified molecular markers.

**Table 1V** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has rheumatoid arthritis as compared to a second trait subgroup wherein each member of the second trait subgroup does not have rheumatoid arthritis using the

ChondroChip™ platform . The table also shows the sequences of selected products of the identified molecular markers.

5       **Table 1W** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has rheumatoid arthritis as compared to a second trait subgroup wherein each member of the second trait subgroup does not have rheumatoid arthritis using the Affymetrix® platform . The table also shows the sequences of selected products of the identified molecular markers.

10       **Table 1X** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has depression as compared with a second trait subgroup wherein each member of the second trait subgroup does not having depression using the ChondroChip™ platform. The table also shows the sequences of selected products of the identified molecular markers.

15       **Table 1Y** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has one of various stages of osteoarthritis as compared with a second trait subgroup wherein each member of the second trait subgroup does not have osteoarthritis using the ChondroChip™ platform. The table also shows the sequences of selected products of the identified molecular markers.

20       **Table 1Z** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has liver cancer as compared with a second trait subgroup wherein each member of the second trait subgroup does not have liver cancer using the ChondroChip™ platform. The table also shows the sequences of selected products of the identified molecular markers.

25       **Table 1Z(B)** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has liver cancer as compared with a second trait subgroup wherein each member of the second trait subgroup does not have liver cancer using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

30       **Table 1AA** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member

of the subgroup has schizophrenia as compared with a second trait subgroup wherein each member of the second trait subgroup does not have schizophrenia using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

5        **Table 1AB** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has Chagas disease as compared with a second trait subgroup wherein each member of the second trait subgroup does not have Chagas disease using the Affymetrix® platform. The table also shows the sequences of selected products of the  
10 identified molecular markers.

**Table 1AC** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has both asthma and osteoarthritis as compared a second trait subgroup wherein each member of the second trait subgroup has only osteoarthritis using the  
15 ChondroChip™. The table also shows the sequences of selected products of the identified molecular markers.

**Table 1AD** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has asthma as compared with a second trait subgroup wherein each  
20 member of the second trait subgroup does not have asthma using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 1AE** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member  
25 of the subgroup has lung cancer as compared with a second trait subgroup wherein each member of the second trait subgroup does not have lung cancer using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 1AG** shows the molecular markers that are differentially expressed in blood  
30 samples from a training population comprised of a first trait subgroup where each member of the subgroup has hypertension as compared with a second trait subgroup wherein each member of the second trait subgroup does not have hypertension using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 1AH** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has obesity as compared with a second trait subgroup wherein each member of the second trait subgroup does not have obesity using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 1AI** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has ankylosing spondylitis as compared with a second trait subgroup wherein each member of the second trait subgroup does not have ankylosing spondylitis using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 2** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has either mild or severe OA, but for which molecular markers relevant to asthma, obesity, hypertension, systemic steroids and allergies have been removed. The table also shows the sequences of selected products of the identified molecular markers.

**Table 3** is a group of tables wherein each table shows those molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has a first disease as compared to blood samples from a second trait subgroup wherein each member of the second trait subgroup has a second disease so as to allow differential diagnosis as between said first and second disease.

**Table 3A** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has schizophrenia as compared with a second trait subgroup wherein each member of the second trait subgroup has manic depression syndrome (MDS) using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 3B** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has hepatitis as compared with a second trait subgroup wherein each member of the second trait subgroup has liver cancer using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 3C** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has bladder cancer as compared with a second trait subgroup wherein each member of the second trait subgroup has liver cancer using the Affymetrix® platform. The  
5 table also shows the sequences of selected products of the identified molecular markers.

**Table 3D** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has bladder cancer as compared with a second trait subgroup wherein each member of the second trait subgroup has testicular cancer using the Affymetrix® platform.  
10 The table also shows the sequences of selected products of the identified molecular markers.

**Table 3E** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has testicular cancer as compared with a second trait subgroup wherein each  
15 member of the second trait subgroup has kidney cancer using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 3F** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has liver cancer as compared with a second trait subgroup wherein each member  
20 of the second trait subgroup has stomach cancer using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 3G** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has liver cancer as compared with a second trait subgroup wherein each member  
25 of the second trait subgroup has colon cancer using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 3H** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has stomach cancer as compared with a second trait subgroup wherein each  
30 member of the second trait subgroup has colon cancer using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 3I** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has Rheumatoid Arthritis as compared with a second trait subgroup wherein each member of the second trait subgroup has Osteoarthritis using the Affymetrix® platform.

5 The table also shows the sequences of selected products of the identified molecular markers.

**Table 3K** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has Chagas Disease as compared with a second trait subgroup wherein each member of the second trait subgroup has Heart Failure using the Affymetrix® platform.

10 The table also shows the sequences of selected products of the identified molecular markers.

**Table 3L** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has Chagas Disease as compared with a second trait subgroup wherein each member of the second trait subgroup has Coronary Artery Disease using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

15

**Table 3N** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has Coronary Artery Disease as compared with a second trait subgroup wherein each member of the second trait subgroup has Heart Failure using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

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**Table 3P** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has Asymptomatic Chagas Disease as compared with a second trait subgroup wherein each member of the second trait subgroup has Symptomatic Chagas Disease using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

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**Table 3Q** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has Alzheimer's' as compared with a second trait subgroup wherein each member of the second trait subgroup has Schizophrenia using the Affymetrix® platform.



The table also shows the sequences of selected products of the identified molecular markers.

5       **Table 3R** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has Alzheimer's' as compared with a second trait subgroup wherein each member of the second trait subgroup has Manic Depression Syndrome using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

10       **Table 4** tables are those which shows molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has a stage of Osteoarthritis as compared to blood samples from a second trait subgroup wherein each member of the second trait subgroup has a second stage of Osteoarthritis so as to allow monitoring of progression and/or regression of disease. Each table also shows the sequences of selected products of the identified molecular markers.

15       **Table 4A** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has Osteoarthritis as compared with a second trait subgroup wherein each member of the second trait subgroup is without Osteoarthritis using the ChondroChip™ platform. The table also shows the sequences of selected products of the identified molecular markers.

20       **Table 4B** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has Osteoarthritis as compared with a second trait subgroup wherein each member of the second trait subgroup is without Osteoarthritis using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

25       **Table 4C** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has mild Osteoarthritis as compared with a second trait subgroup wherein each member of the second trait subgroup is without mild Osteoarthritis using the ChondroChip™ platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 4D** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has mild Osteoarthritis as compared with a second trait subgroup wherein each member of the second trait subgroup is without Osteoarthritis using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 4E** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has moderate Osteoarthritis as compared with patients without Osteoarthritis using the ChondroChip™ platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 4F** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has moderate Osteoarthritis as compared a second trait subgroup wherein each member of the second trait subgroup is without Osteoarthritis using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 4G** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has marked Osteoarthritis as compared with a second trait subgroup wherein each member of the second trait subgroup is without Osteoarthritis using the ChondroChip™ platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 4H** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has marked Osteoarthritis as compared with a second trait subgroup wherein each member of the second trait subgroup is without Osteoarthritis using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 4I** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has severe Osteoarthritis as compared with a second trait subgroup wherein each member of the second trait subgroup is without Osteoarthritis using the ChondroChip™

platform. The table also shows the sequences of selected products of the identified molecular markers.

5       **Table 4J** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has severe Osteoarthritis as compared with a second trait subgroup wherein each member of the second trait subgroup is without Osteoarthritis using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

10       **Table 4K** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has mild Osteoarthritis as compared with a second trait subgroup wherein each member of the second trait subgroup has moderate Osteoarthritis using the ChondroChip™ platform. The table also shows the sequences of selected products of the identified molecular markers.

15       **Table 4L** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has mild Osteoarthritis as compared with a second trait subgroup wherein each member of the second trait subgroup has moderate Osteoarthritis using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

20       **Table 4M** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has mild Osteoarthritis as compared with a second trait subgroup wherein each member of the second trait subgroup has marked Osteoarthritis using the ChondroChip™ platform. The table also shows the sequences of selected products of the identified molecular markers.

25       **Table 4N** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has mild Osteoarthritis as compared with a second trait subgroup wherein each member of the second trait subgroup has marked Osteoarthritis using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

30       **Table 4O** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the

subgroup has mild Osteoarthritis as compared with a second trait subgroup wherein each member of the second trait subgroup has severe Osteoarthritis using the ChondroChip™ platform. The table also shows the sequences of selected products of the identified molecular markers.

5       **Table 4P** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has mild Osteoarthritis as compared with a second trait subgroup wherein each member of the second trait subgroup has severe Osteoarthritis using the Affymetrix® platform. The table also shows the sequences of selected products of the identified  
10       molecular markers.

**Table 4Q** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has moderate Osteoarthritis as compared with a second trait subgroup wherein each member of the second trait subgroup has marked Osteoarthritis using the  
15       ChondroChip™ platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 4R** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has moderate Osteoarthritis as compared with a second trait subgroup wherein  
20       each member of the second trait subgroup has marked Osteoarthritis using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 4S** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the  
25       subgroup has moderate Osteoarthritis as compared with patients a second trait subgroup wherein each member of the second trait subgroup has severe Osteoarthritis using the ChondroChip™ platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 4T** shows the molecular markers that are differentially expressed in blood  
30       from a training population comprised of a first trait subgroup where each member of the subgroup has moderate Osteoarthritis as compared with a second trait subgroup wherein each member of the second trait subgroup has severe Osteoarthritis using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 4U** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has marked Osteoarthritis as compared with a second trait subgroup wherein each member of the second trait subgroup has severe Osteoarthritis using the ChondroChip™ platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 4V** shows the molecular markers that are differentially expressed in blood from a training population comprised of a first trait subgroup where each member of the subgroup has marked Osteoarthritis as compared with a second trait subgroup wherein each member of the second trait subgroup has severe Osteoarthritis using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 5** tables are those which identify molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has a disease or condition of interest as compared to blood samples from a second trait subgroup wherein each member of the second trait subgroup is without said disease or condition. The tables also shows the sequences of selected products of the identified molecular markers.

**Table 5A** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has psoriasis as compared with a second trait subgroup wherein each member of the second trait subgroup does not have psoriasis using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 5B** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has thyroid disorder as compared with a second trait subgroup wherein each member of the second trait subgroup does not have thyroid disorder using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 5C** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has irritable bowel syndrome as compared with a second trait subgroup wherein each member of the second trait subgroup does not have irritable bowel syndrome

using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

5       **Table 5D** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has osteoporosis as compared with a second trait subgroup wherein each member of the second trait subgroup does not have osteoporosis using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

10       **Table 5E** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has migraine headaches as compared with a second trait subgroup wherein each member of the second trait subgroup does not have migraine headaches using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

15       **Table 5F** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has eczema as compared with a second trait subgroup wherein each member of the second trait subgroup does not have eczema using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

20       **Table 5G** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has NASH as compared with a second trait subgroup wherein each member of the second trait subgroup does not have NASH using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

25       **Table 5H** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has Alzheimer's disease as compared with a second trait subgroup wherein each member of the second trait subgroup does not have Alzheimer's disease using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

30       **Table 5I** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member

of the subgroup has Manic Depression Syndrome as compared with a second trait subgroup wherein each member of the second trait subgroup does not have Manic Depression Syndrome using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

5        **Table 5J** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has Crohn's Colitis as compared with a second trait subgroup wherein each member of the second trait subgroup does not have Crohn's Colitis using the Affymetrix® platform. The table also shows the sequences of selected products of the  
10 identified molecular markers.

**Table 5K** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has Chronic Cholecystitis as compared with a second trait subgroup wherein each member of the second trait subgroup does not have Chronic Cholecystitis  
15 using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 5L** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has Heart Failure as compared with a second trait subgroup wherein each  
20 member of the second trait subgroup does not have Heart Failure using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 5M** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member  
25 of the subgroup has Cervical Cancer as compared with a second trait subgroup wherein each member of the second trait subgroup does not have Cervical Cancer using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 5N** shows the molecular markers that are differentially expressed in blood  
30 samples from a training population comprised of a first trait subgroup where each member of the subgroup has Stomach Cancer as compared with a second trait subgroup wherein each member of the second trait subgroup does not have Stomach Cancer using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 5O** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has Kidney Cancer as compared with a second trait subgroup wherein each member of the second trait subgroup does not have Kidney Cancer using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 5P** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has Testicular Cancer as compared with a second trait subgroup wherein each member of the second trait subgroup does not have Testicular Cancer using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 5Q** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has Colon Cancer as compared a second trait subgroup wherein each member of the second trait subgroup does not have Colon Cancer using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 5R** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has Hepatitis B as compared with a second trait subgroup wherein each member of the second trait subgroup does not have Hepatitis B using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 5S** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has Pancreatic Cancer as compared with a second trait subgroup wherein each member of the second trait subgroup does not have Pancreatic Cancer using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 5T** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has Asymptomatic Chagas as compared with a second trait subgroup wherein each member of the second trait subgroup does not have Chagas using the



Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

5       **Table 5U** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has Symptomatic Chagas as compared with a second trait subgroup wherein each member of the second trait subgroup does not have Chagas using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

10       **Table 5V** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has Bladder Cancer as compared with patients not having Bladder Cancer using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

15       **Table 6** tables are those tables which show those molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has any one of a series of related conditions as compared to blood samples a second trait subgroup wherein each member of the second trait subgroup does not have said related conditions. The table also shows the sequences of selected products of the identified molecular markers.

20       **Table 6A** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has Cancer as compared with a second trait subgroup wherein each member of the second trait subgroup does not have Cancer using the Affymetrix® platform. The table also shows the sequences of selected products of the identified  
25       molecular markers.

30       **Table 6B** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup with Cardiovascular Disease as compared with a second trait subgroup wherein each member of the second trait subgroup does not have a Cardiovascular Disease using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 6C** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup has a Neurological Disease as compared with a second trait subgroup

wherein each member of the second trait subgroup does not have a Neurological Disease using the Affymetrix® platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 7** tables are those tables which show molecular markers that are  
5 differentially expressed in blood samples from with a condition wherein said condition is a treatment as compared to blood samples from patients without said treatment or with a different said treatment.

**Table 7A** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member  
10 of the subgroup is taking Celebrex® as compared a second trait subgroup wherein each member of the second trait subgroup is taking a Cox Inhibitor which was not Celebrex® using the ChondroChip™ platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 7B** shows the molecular markers that are differentially expressed in blood  
15 samples from a training population comprised of a first trait subgroup where each member of the subgroup is taking Celebrex® as compared with a second trait subgroup wherein each member of the second trait subgroup is not taking Celebrex® using the ChondroChip™ platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 7C** shows the molecular markers that are differentially expressed in blood  
20 samples from a training population comprised of a first trait subgroup where each member of the subgroup is taking Vioxx® as compared a second trait subgroup wherein each member of the second trait subgroup is not taking Vioxx® using the ChondroChip™ platform. The table also shows the sequences of selected products of the identified  
25 molecular markers.

**Table 7D** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup is taking Vioxx® as compared with a second trait subgroup wherein each member of the second trait subgroup on a Cox inhibitor but not on Vioxx® using the  
30 ChondroChip™ platform. The table also shows the sequences of selected products of the identified molecular markers.

**Table 7E** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup is taking NSAIDS as compared with patients not on NSAIDS using the

ChondroChip™ platform. The table also shows the sequences of selected products of the identified molecular markers.

5       **Table 7F** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup is taking Cortisone as compared with a second trait subgroup wherein each member of the second trait subgroup on not on Cortisone using the ChondroChip™ platform. The table also shows the sequences of selected products of the identified molecular markers.

10       **Table 7G** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup is taking Visco Supplement as compared with a second trait subgroup wherein each member of the second trait subgroup not on Visco Supplement using the ChondroChip™ platform. The table also shows the sequences of selected products of the identified molecular markers.

15       **Table 7H** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup is taking Lipitor® as compared with a second trait subgroup wherein each member of the second trait subgroup not on Lipitor® using the ChondroChip™ platform. The table also shows the sequences of selected products of the identified molecular markers.

20       **Table 7I** shows the molecular markers that are differentially expressed in blood samples from a training population comprised of a first trait subgroup where each member of the subgroup is who are smokers as compared with a second trait subgroup wherein each member of the second trait subgroup who are not smokers using the ChondroChip™ platform. The table also shows the sequences of selected products of the identified molecular markers.

25       To further clarify, Tables 1AA; 1AB; 1AD; 1AE; 1AG; 1AH; 1AT; 1S; 1T; 1U; 1W; 1Z(b); 3A; 3B; 3C; 3D; 3E; 3F; 3G; 3H; 3I; 3K; 3L; 3P; 3Q; 3R; 4B; 4D; 4F; 4H; 4J; 4L; 4N; 4P; 4R; 4T; 4V; 5A; 5B; 5C; 5D; 5EE; 5F; 5G; 5H; 5I; 5J; 5K; 5L; 5M; 5N; 5O; 30   5P 5Q; 5R; 5S; 5T; 5U; 5V; 6A; 6B; 6C; 7F; and 7G each identify the molecular markers identified using the Affymetrix® genechip to screen the products of the majority of molecular markers of the human genome in accordance with step 202.

Tables 1A; 1 AC; 1B; 1C; 1D; 1E; 1F; 1G; 1H; 1I; 1J; 1K; 1L; 1M; 1N; 1O; 1P; 1Q; 1R; 1V; 1X; 1Y; 1Z; 2; 4A; 4C; 4E; 4G; 4I; 4K; 4M; 4O; 4Q; 4S; 4V; 7A; 7B; 7C;

7D; 7E; 7H; and 7I each identify molecular markers identified using our own ChondroChip™ genechip to screen the products of the majority of the molecular markers of the human genome.

Like reference numerals refer to corresponding parts throughout the several views  
5 of the drawings.

## 5. DETAILED DESCRIPTION

The embodiments of the present invention use novel approaches to screen and select molecular markers and develop classifiers that can be used to harness the use of molecular marker data from blood. The present invention thus provides systems and  
10 methods for constructing biological classifiers using molecular marker data from blood by providing a method to screen and select from a large variety of potential molecular markers so as to identify a small subset of molecular markers. The classifiers and the combinations of molecular markers identified using aspects of the current invention are useful for a wide variety of purposes including: diagnosis; prognosis; prediction of disease,  
15 stage of disease or disease risk; monitoring disease progression and/or regression; monitoring disease reoccurrence and identifying risk of disease reoccurrence; determining and/or predicting response to treatment and/or treatment outcomes; monitoring and/or predicting treatment compliance or non-compliance and the like. As used herein, a “condition” includes a mode or state of being including a physical, emotional,  
20 psychological or pathological state. A condition can be as a result of both “genetic” (ie genetically inherited) and/or “environmental” factors (ie the result of exposure to internal or external influences). In one embodiment of the invention, a condition is a disease. In another embodiment of the invention, a condition is a stage of a disease. In yet another embodiment of the invention, a condition is a mode or state of being which is not a  
25 disease. For example in one embodiment, a condition which is not a disease is a condition resulting from the progression of time. A condition resulting from progression of time can include, but is not limited to: memory loss, loss of skin elasticity, loss of muscle tone, and loss of sexual desire. In a further embodiment of the invention a condition which is not a disease is the response to treatment. A treatment can include, but is not limited to disease  
30 modifying treatments as well as treatments useful in mitigating the symptoms of disease. For example treatments can include drugs specific for a disease of the invention.

As used herein, the term “data” or “molecular marker data” generally refers to data reflective of the abundance of a product of a molecular marker in blood including either or both of RNA and protein.

As used herein, “diagnosis” includes the ability to determine that an individual has or does not have a specific condition or conditions. Diagnosis also refers to the ability to determine that an individual has one condition or conditions as compared with one or more other condition or conditions. In some embodiments, diagnosis refers to the ability to demonstrate an increased likelihood that an individual has a specific condition.

“diagnosis” refers to the ability to demonstrate an increased likelihood that an individual has one condition as compared to a second condition. More particularly “diagnosis” refers to a process whereby there is an increased likelihood that an individual is properly characterized as having a condition (“true positive”) or is properly characterized as not having a condition (or is properly characterized as having the second condition where the diagnosis is as between two conditions) (“true negative”) while minimizing the likelihood that the individual is improperly characterized with said condition (“false positive”) or improperly characterized as not being afflicted with said condition (or improperly characterized as having the second condition)(“false negative”).

As used herein, the term “differential expression” refers to a difference in the level of expression of the RNA and/or protein products of a molecular marker of the invention, as measured by the amount or level of RNA or protein. In reference to RNA, it can include difference in the level of expression of mRNA, and/or one or more spliced variants of mRNA of the biomarker in one sample as compared with the level of expression of the same one or more biomarkers of the invention as measured by the amount or level of RNA, including mRNA and/or one or more spliced variants of mRNA in a second sample. “Differentially expressed” or “differential expression” can also include a measurement of the protein, or one or more protein variants encoded by a molecular marker of the invention in a sample or population of samples as compared with the amount or level of protein expression, including one or more protein variants of a molecular marker of the invention. Differential expression can be determined as described herein and as would be understood by a person skilled in the art. The term “differentially expressed” or “changes in the level of expression” refers to an increase or decrease in the measurable expression level of a given product of a molecular marker as measured by the amount of RNA and/or the amount of protein in a sample as compared with the measurable expression level of a given product of the molecular marker in a second sample. The first sample and second sample need not be from different patients, but can be samples from the same patient taken at different time points. The term “differentially expressed” or “changes in the level of expression” can also refer to an increase or decrease in the measurable expression level of

a given molecular marker in a population of samples as compared with the measurable expression level of the molecular marker in a second population of samples. As used herein, "differentially expressed" when referring to a single sample can be measured using the ratio of the level of expression of a given molecular marker in said sample as compared with the mean expression level of the given molecular marker of a control population wherein the ratio is not equal to 1.0. Differentially expressed can also be used to include comparing a first population of samples as compared with a second population of samples or a single sample to a population of samples using either a ratio of the level of expression or using p-value. When using p-value, a nucleic acid transcript including hnRNA and mRNA is identified as being differentially expressed as between a first and second population when the p-value is less than 0.1, less than 0.05, less than 0.01, less than 0.005, less than 0.001 etc. When determining differential expression on the basis of the ratio of the level of molecular marker product – expression of an RNA or protein product of the molecular marker is differentially expressed if the ratio of the level of the RNA or protein product in a first sample as compared with that in a second sample is greater than or less than 1.0. For instance, a ratio of greater than 1, for example 1.2, 1.5, 1.7, 2, 3, 4, 10, 20, or a ratio of less than 1, for example 0.8, 0.6, 0.4, 0.2, 0.1. 0.05, of RNA or protein product of a molecular marker would be indicative of differential expression. In another embodiment of the invention, a molecular marker is differentially expressed if the mean level of expression of a nucleic acid transcript including the hnRNA and/or mRNA transcript in a first population as compared with its mean level of expression of the transcript in a second population is greater than or less than 1.0. For instance, a ratio of greater than 1, for example 1.2, 1.5, 1.7, 2, 3, 4, 10, 20, or a ratio less than 1, for example 0.8, 0.6, 0.4, 0.2, 0.1. 0.05 would be indicative of differential expression. In another embodiment of the invention a molecular marker is differentially expressed if the ratio of the level of the hnRNA and/or mRNA transcript in a first sample as compared with the mean level of the transcript of the second population is greater than or less than 1.0 and includes for example, a ratio of greater than 1, for instance 1.2, 1.5, 1.7, 2, 3, 4, 10, 20, or a ratio less than 1, for example 0.8, 0.6, 0.4, 0.2, 0.1. 0.05. "Differentially increased expression" refers to 1.1 fold, 1.2 fold, 1.4 fold, 1.6 fold, 1.8 fold, or more, relative to a standard, such as the mean of the expression level of the second population. "Differentially decreased expression" refers to less than 1.0 fold, 0.8 fold, 0.6 fold, 0.4 fold, 0.2 fold, 0.1 fold or less, relative to a standard, such as the mean of the expression level of the second population.

As used herein, the term "molecular marker" (or sometimes referred to as a "biomarker") refers to a gene or a genetic element. In some embodiments, the molecular marker of interest is identified by the Gene ID (formerly Locus Link ID) as is published by the National Center for Biotechnology Information (NCBI) Database as would be understood by a person skilled in the art.

As used herein, the term "oligonucleotide" is defined as a molecule comprised of two or more deoxyribonucleotides and/ or ribonucleotides, and preferably more than three. Its exact size will depend upon many factors which, in turn, depend upon the ultimate function and use of the oligonucleotide. The oligonucleotides may be from about 8 to about 1,000 nucleotides long. Although oligonucleotides of 8 to 100 nucleotides are useful in the invention, preferred oligonucleotides range from about 8 to about 15 bases in length, from about 8 to about 20 bases in length, from about 8 to about 25 bases in length, from about 8 to about 30 bases in length, from about 8 to about 40 bases in length or from about 8 to about 50 bases in length.

The term, "primer", as used herein refers to an oligonucleotide, whether occurring naturally as in a purified restriction digest or produced synthetically, which is capable of acting as a point of initiation of synthesis when placed under conditions in which synthesis of a primer extension product, which is complementary to a nucleic acid strand, is induced, i.e., in the presence of nucleotides and an inducing agent such as a DNA polymerase and at a suitable temperature and pH. The primer may be either single-stranded or double-stranded and must be sufficiently long to prime the synthesis of the desired extension product in the presence of the inducing agent. The exact length of the primer will depend upon many factors, including temperature, source of primer and the method used. For example, for diagnostic applications, depending on the complexity of the target sequence, the oligonucleotide primer typically contains 15-25 or more nucleotides, although it may contain fewer nucleotides. The factors involved in determining the appropriate length of primer are readily known to one of ordinary skill in the art. In general, the design and selection of primers embodied by the instant invention is according to methods that are standard and well known in the art, see Dieffenbach, C.W., Lowe, T.M.J., Dveksler, G.S. (1995) General Concepts for PCR Primer Design. In: PCR Primer, A Laboratory Manual (Eds. Dieffenbach, C.W, and Dveksler, G.S.) Cold Spring Harbor Laboratory Press, New York, 133-155; Innis, M.A., and Gelfand, D.H. (1990) Optimization of PCRs. In: PCR protocols, A Guide to Methods and Applications (Eds. Innis, M.A., Gelfand, D.H., Sninsky, J.J., and White, T.J.) Academic Press, San Diego, 3-12; Sharrocks, A.D. (1994)

The design of primers for PCR. In: PCR Technology, Current Innovations (Eds. Griffin, H.G., and Griffin, A.M, Ed.) CRC Press, London, 5-11.

As used herein, the term "probe" means oligonucleotides and analogs thereof and refers to a range of chemical species that recognise polynucleotide target sequences through hydrogen bonding interactions with the nucleotide bases of the target sequences. The probe or the target sequences may be single- or double-stranded RNA or single- or double-stranded DNA or a combination of DNA and RNA bases. A probe is at least 8 nucleotides in length and less than the length of a complete gene. A probe may be 10, 20, 30, 50, 75, 100, 150, 200, 250, 400, 500 and up to 2000 nucleotides in length. Probes can include oligonucleotides modified so as to have a tag which is detectable by fluorescence, chemiluminescence and the like. The probe can also be modified so as to have both a detectable tag and a quencher molecule, for example Taqman® and Molecular Beacon® probes.

As used herein, the term "product of the molecular marker" or "molecular marker product" refers to the RNA or protein found in blood which corresponds to the molecular marker (ie is transcribed from the gene or genetic element or is translated from RNA which is transcribed from the gene or genetic element). For example, in some embodiments RNA resulting from the molecular marker can include one or more of the following species; hnRNA, mRNA, and/or one or more spliced variants of mRNA. In some embodiments, proteins resulting from the molecular marker can include any proteins found in blood which correspond to the RNA resulting from the molecular marker.

As used herein, the term "selectively amplified" or "selective amplification", refers to a process whereby one or more copies of a particular target nucleic acid sequence is selectively generated from a template nucleic acid. Selective amplification or selectively amplified is to be compared with amplification in general which can be used as a method in combination with, for example, random primers and an oligodT primer to amplify a population of nucleic acid sequences (e.g. mRNA). Selective amplification is preferably done by the method of polymerase chain reaction (Mullis and Faloona, 1987, Methods Enzymol. 155:335).

As used herein, the term "selectively binds" in the context of proteins encompassed by the invention refers to the specific interaction of any two of a peptide, a protein, a polypeptide, and an antibody, wherein the interaction preferentially occurs as between any two of a peptide, protein, polypeptide and antibody preferentially as compared with any other peptide, protein, polypeptide and antibody. For example, when the two molecules



are protein molecules, a structure on the first molecule recognises and binds to a structure on the second molecule, rather than to other proteins. "Selective binding", "Selective binding", as the term is used herein, means that a molecule binds its specific binding partner with at least 2-fold greater affinity, and preferably at least 10-fold, 20-fold, 50-fold, 100-fold or higher affinity than it binds a non-specific molecule.

As used herein "selective hybridization" in the context of this invention refers to a hybridization which occurs as between a polynucleotide encompassed by the invention and an RNA, and its complement thereof (ie a cDNA copy), of the molecular marker of the invention, wherein the hybridization is such that the polynucleotide preferentially binds to the RNA products of the molecular marker of the invention relative to the RNA products of other molecular markers or other genes in the genome in question. In a preferred embodiment a polynucleotide which "selectively hybridizes" is one which hybridizes with a selectivity of greater than 70%, greater than 80%, greater than 90% and most preferably of 100% (i.e. cross hybridization with other RNA species preferably occurs at less than 30%, less than 20%, less than 10%). As would be understood to a person skilled in the art, a polynucleotide which "selectively hybridizes" to the RNA product of a biomarker of the invention can be determined taking into account the length and composition.

As used herein, "specifically hybridizes", "specific hybridization" refers to hybridization which occurs when two nucleic acid sequences are substantially complementary (at least about 65% complementary over a stretch of at least 14 to 25 nucleotides, preferably at least about 75% complementary, more preferably at least about 90% complementary). See Kanehisa, M., 1984, Nucleic acids Res., 12:203, incorporated herein by reference. As a result, it is expected that a certain degree of mismatch is tolerated. Such mismatch may be small, such as a mono-, di- or tri-nucleotide. Alternatively, a region of mismatch can encompass loops, which are defined as regions in which there exists a mismatch in an uninterrupted series of four or more nucleotides. Numerous factors influence the efficiency and selectivity of hybridization of two nucleic acids, for example, the hybridization of a nucleic acid member on an array to a target nucleic acid sequence. These factors include nucleic acid member length, nucleotide sequence and/or composition, hybridization temperature, buffer composition and potential for steric hindrance in the region to which the nucleic acid member is required to hybridize. A positive correlation exists between the nucleic acid length and both the efficiency and accuracy with which a nucleic acid will anneal to a target sequence. In particular, longer sequences have a higher melting temperature (TM) than do shorter ones,

and are less likely to be repeated within a given target sequence, thereby minimizing non-specific hybridization. Hybridization temperature varies inversely with nucleic acid member annealing efficiency. Similarly the concentration of organic solvents, e.g., formamide, in a hybridization mixture varies inversely with annealing efficiency, while increases in salt concentration in the hybridization mixture facilitate annealing. Under stringent annealing conditions, longer nucleic acids, hybridize more efficiently than do shorter ones, which are sufficient under more permissive conditions.

As used herein, the term "specifically binds" refers to the interaction of two molecules, e.g., a ligand and a protein or peptide, or an antibody and a protein or peptide wherein the interaction is dependent upon the presence of particular structures on the respective molecules. For example, when the two molecules are protein molecules, a structure on the first molecule recognises and binds to a structure on the second molecule, rather than to proteins in general. "Specific binding", as the term is used herein, means that a molecule binds its specific binding partner with at least 2-fold greater affinity, and preferably at least 10-fold, 20-fold, 50-fold, 100-fold or higher affinity than it binds a non-specific molecule.

As herein used, the term "standard stringent conditions" and "stringent conditions" means hybridization will occur only if there is at least 95% and preferably, at least 97% identity between the sequences, wherein the region of identity comprises at least 10 nucleotides. In one embodiment, the sequences hybridize under stringent conditions following incubation of the sequences overnight at 42°C, followed by stringent washes (0.2X SSC at 65°C). The degree of stringency of washing can be varied by changing the temperature, pH, ionic strength, divalent cation concentration, volume and duration of the washing. For example, the stringency of hybridization may be varied by conducting the hybridization at varying temperatures below the melting temperatures of the probes. The melting temperature of the probe may be calculated using the following formulas:

For oligonucleotide probes, between 14 and 70 nucleotides in length, the melting temperature ( $T_m$ ) in degrees Celcius may be calculated using the formula:  
$$T_m = 81.5 + 16.6(\log [Na^+]) + 0.41(\text{fraction G+C}) - (600/N)$$
 where N is the length of the oligonucleotide.

For example, the hybridization temperature may be decreased in increments of 5°C from 68°C to 42°C in a hybridization buffer having a  $Na^+$  concentration of approximately 1M. Following hybridization, the filter may be washed with 2X SSC, 0.5% SDS at the

temperature of hybridization. These conditions are considered to be “moderate stringency” conditions above 50°C and “low stringency” conditions below 50°C. A specific example of “moderate stringency” hybridization conditions is when the above hybridization is conducted at 55°C. A specific example of “low stringency” hybridization conditions is  
5 when the above hybridization is conducted at 45°C.

If the hybridization is carried out in a solution containing formamide, the melting temperature of the annealing nucleic acid strands may be calculated using the equation  $T_m = 81.5 + 16.6(\log [Na^+]) + 0.41(\text{fraction G + C}) - (0.63\% \text{ formamide}) - (600/N)$ , where N is the length of the probe.

10 If the hybridization is carried out in a solution containing formamide, the melting temperature of the annealing nucleic acid strands may be calculated using the equation  $T_m = 81.5 + 16.6(\log [Na^+]) + 0.41(\text{fraction G + C}) - (0.63\% \text{ formamide}) - (600/N)$ , where N is the length of the probe.

For example, the hybridization may be carried out in buffers, such as 6X SSC,  
15 containing formamide at a temperature of 42°C. In this case, the concentration of formamide in the hybridization buffer may be reduced in 5% increments from 50% to 0% to identify clones having decreasing levels of homology to the probe. Following hybridization, the filter may be washed with 6X SSC, 0.5% SDS at 50 °C. Hybridization conditions are considered to be “moderate stringency” conditions when hybridization  
20 fluids are comprised of above 25% formamide and “low stringency” conditions when hybridization fluids are comprised of below 25% formamide. A specific example of “moderate stringency” hybridization conditions is when the above hybridization is conducted at 30% formamide. A specific example of “low stringency” hybridization conditions is when the above hybridization is conducted at 10% formamide.

25 As used herein, the term “responder” is used to mean an individual who responds to treatment. The use of the term “responds to treatment” depends upon the context of the treatment and the disease or condition, but in some embodiments indicate a sufficiently effective and safe response by an individual to the administration of treatment.

As used herein, the term “non-responder” is used to mean an individual who does  
30 not respond positively to treatment. The use of the phrase “does not respond to treatment” also depends upon the context of the treatment and the disease or condition, but in some embodiments indicates an ineffective or unsafe response by an individual to the administration of treatment.

As used herein, the term “trait” is a mode or state of being including a physical, emotional, psychological or pathological state. A trait can include both “genetic” and/or “environmentally” influenced factors. The term “genetic factors” means genetically inherited elements which affect one or more traits as a result of the genetic makeup of the individual. The term “environmental factors” includes exposure to internal or external influences including but not limited to medical treatments, non-medical drugs, pollution, environmental toxins, lead poisoning, mercury poisoning, exposure to genetically modified organisms, radioactivity, pesticides, insecticides, cigarette smoke, alcohol, or exercise and can affect abundance of RNA or affect gene expression as a result of epigenetic mutations and/or non genetic mutations. A physiological or pathological trait can include the status with regards to a condition including having a condition including a disease, having risk factors of a disease having a certain stage of disease or having a certain response to treatment or a risk of a certain response to treatment. In some cases a displayed trait can actually be the result of one or more underlying traits. A trait also includes clinically measurable parameters including those clinically measurable parameters which are indicators of state of health or disease. For example, a clinically measurable parameter includes blood pressure, lung capacity, electrolyte level, enzyme levels (e.g. Serum Glutamic Oxaloacetic Transaminase, alkaline phosphatase, Gamma-Glutamyltransferase or Gamma-Glutamyl Transpeptidase, Lactic dehydrogenase) hormone levels (e.g. thyroid stimulating hormone); protein levels (e.g. Prostate specific antigen PSA) and the like. Clinically measurable parameters can include disease specific clinical indicators, for example prostate specific antigen as an indicator of prostate cancer; insulin levels as an indicator of diabetes; thyroid stimulating hormone levels as an indicator of thyroid disorder and the like.

As used herein, the term “trait subgroup” is used to define a group of subjects where each subject has at least one trait or group of traits in common, for example, each subject has a disease, a specific stage of disease, same response to treatment, taking the same drug, etc.

As used herein, the terms “treatment”, “treat”, and “treating” includes administration of one or more compounds, combination of one or more compounds, application of a non-compound based therapeutic regimen, or any combination thereof where administration includes application of a single treatment, a regiment or course of treatment etc. to reduce or amelioration of the progression, severity and/or duration of a

disease or condition and/or the reduction or amelioration of the symptoms of a disease or condition resulting from the use of a treatment and/or treatment regime.

## 5.1 INVENTIVE SYSTEMS AND ALGORITHMS

Fig. 1 shows an exemplary system according to an embodiment of the invention  
5 that supports the functionality described herein. The system is preferably a computer system 10 having:

- one or more central processors 22;
- a main non-volatile storage unit 14, for example a hard disk drive, for storing software and data, the storage unit 14 controlled by storage  
10 controller 12;
- a system memory 36, preferably high speed random-access memory (RAM), for storing system control programs, data, and application programs, comprising programs and data loaded from non-volatile storage unit 14; system memory 36 may also include read-only memory (ROM);
- 15 • an optional user interface 32, comprising one or more input devices (e.g., keyboard 28) and a display 26 or other output device;
- an optional network interface card 20 for connecting to any wired or wireless communication network 34 (e.g., a wide area network such as the Internet);
- 20 • an internal bus 30 for interconnecting the aforementioned elements of the system; and
- a power source 24 to power the aforementioned elements.

Operation of computer 10 is controlled primarily by operating system 40, which is executed by central processing unit 22. Operating system 40 can be stored in system  
25 memory 36. In addition to operating system 40, in a typical implementation, system memory 36 includes various components described below. Those of skill in the art will appreciate that such components can be wholly resident in RAM 36 or non-volatile storage unit 14. Furthermore, at any given time, such components can partially reside both in RAM 36 and non-volatile storage unit 14. Further still, some of the components shown in  
30 Fig. 1 as being resident in RAM 36 can be resident in another computer (a remote computer) that is addressable by computer 10 over wide area network 34. It will be appreciated that such a remote computer may physically be resident in the same room as computer 10 or in another physical location. As illustrated in Fig. 1, in one exemplary

embodiment of the invention, RAM 36 comprises programs and data to interact with components in the computer system 10 for configuring:

- file system 42 for controlling access to the various files and data structures used by embodiments of the present invention;
- 5 • a training population 44 for use in construction of one or more classifiers ;
- a molecular marker data processing module I- 54 for processing molecular marker data representative of a genome or a portion thereof for members of training population 44;
- 10 • a molecular marker screening module A (56A) for identifying molecular markers whose molecular marker data individually discriminates between two or more trait subgroups of the training population using molecular marker data of module 54;
- a molecular marker screening module B (56B) for identifying molecular markers whose molecular marker data do not individually discriminate, but  
15 demonstrate ability to differentiate between two or more trait subgroups of the training population when used in combination using molecular marker data of module 54;
- a candidate molecular marker data structure 58 for storing information about candidate molecular markers identified by molecular marker  
20 candidate screening module 56A and optionally molecular marker candidate screening module 56B;
- a second molecular marker data processing module II 61 for processing additional molecular marker data for a selection of the candidate molecular markers identified in screening module 56A and, optionally, screening  
25 module 56B for members of a training population;
- an outlier selection module 57 for evaluating molecular marker data identified in either module 56A and/or 56B or module 61 so as to remove one or more individuals from the training population as outliers;
- a combination module 61-5 which selects combinations of molecular  
30 markers from candidate molecular markers identified in module 56A and optionally module 56B
- a molecular marker classifier construction module 62 for constructing candidate classifiers from combinations of molecular markers identified by molecular marker combination module 61-5;

- a molecular marker classifier evaluation module 64 for evaluating and selecting candidate classifiers constructed by molecular marker construction module 62;
- 5 • a classifier polling and reporting module 66 for receiving patient or subject molecular marker data and polling one or more classifiers selected by evaluation module 64 in order to determine whether a patient or subject has the disease or trait associated with each of the respective classifiers;
- a patient database 68 for storage of molecular marker data for diagnostic, prognostic or predictive use; and
- 10 • a classifier database 70 for storage of one or more classifiers selected by molecular marker classifier evaluation module 64.

As illustrated in Fig. 1, computer 10 comprises software program modules and data structures. The data structures either stored in computer 10 or accessible to computer 10 include a training population 44, candidate molecular marker data structures 58, patient  
15 database 68, and classifier database 70. Each of these data structures can comprise any form of data storage system including, but not limited to, a flat ASCII or binary file, an Excel spreadsheet, a relational database (*e.g.* SQL), or an on-line analytical processing (OLAP) database (MDX and/or variants thereof). In some specific embodiments, such data structures are each in the form of one or more databases that include hierarchical  
20 structure (*e.g.*, a star schema). In some embodiments, such data structures are each in the form of databases that do not have explicit hierarchy (*e.g.*, dimension tables that are not hierarchically arranged).

In some embodiments, each of the data structures stored or accessible to system 10 are single data structures. In other embodiments, such data structures in fact comprise a  
25 plurality of data structures (*e.g.*, databases, files, archives) that may or may not all be hosted by the same computer 10. For example, in some embodiments, training population 44 comprises a plurality of Excel spreadsheets that are stored either on computer 10 and/or on computers that are addressable by computer 10 across wide area network 34. In another example, patient database 68 comprises a database that is either stored on  
30 computer 10 or is distributed across one or more computers that are addressable by computer 10 across wide area network 34. Section 5.9 describes exemplary architectures for training population 44, candidate molecular marker data structure 58, patient database 68, and/or classifier database 70.

It will be appreciated that many of the modules and data structures illustrated in Fig. 1 can be located on one or more remote computers. For example, some embodiments of the present application are web service-type implementations. In such embodiments, classifier polling and reporting module 66 and other modules can be used by a physician to treat a patient and can reside on a client computer that is in communication with computer 10 via network 34. In some embodiments, for example, classifier polling and reporting module 66 can be an interactive web page.

In some embodiments, training population 44, candidate molecular marker data structure 58, patient database 68 and/or classifier database 70 and modules (*e.g.* modules 54, 56A, 56B, 57, 61, 61-5, 62, 64, and 66) illustrated in Fig. 1 are on a single computer (computer 10) and in other embodiments one or more of such data structures and module are hosted by one or more remote computers (not shown). Any arrangement of the data structures and software modules illustrated in Fig. 1 on one or more computers is within the scope of the present invention so long as these data structures and software modules are addressable with respect to each other across network 34 or by other electronic means. Thus, the present invention fully encompasses a broad array of computer systems.

Now that an overview of a system in accordance with one embodiment of the present invention has been described, various advantageous methods in accordance with embodiments of the present invention will now be disclosed in conjunction with Figs. 2 through 5. Figure 2 is a flowchart showing a method of selecting molecular markers and developing one or more classifiers or groups of classifiers according to an embodiment of the invention.

#### *Step 202.*

Referring to Fig. 2A, in step 202, molecular marker data reflective of the abundance of each of a plurality of RNA and/or proteins found in the blood for members of training population 44 is obtained using one or more of the techniques as described in Section 5.3 and/or 5.4. In some embodiments, the data is reflective of the abundance of RNA products of the molecular marker. In some embodiments, the RNA products are those expressed in blood. In other embodiments, the RNA products are those which are found in blood, but may not necessarily be expressed in blood (*e.g.* in instances where sufficient mRNA is transported into the blood to be detected. In some embodiments, the data is reflective of the abundance of protein products of the molecular markers. In some embodiments, the data is reflective of the level of proteins expressed in blood. In other embodiments, the data is reflective of proteins found in blood in sufficient quantity to be



detected. Measuring of molecular marker data (ie data reflective of the level of the product of the molecular marker) can be done using those techniques known to persons skilled in the art. Note that in some embodiments, data may be obtained using public sources or other sources of data rather than performing one or more of the techniques described. For  
5 example, it is anticipated that databases of microarray data collected from blood may be available in future.

In some embodiments, the molecular marker data for each molecular marker is obtained using the same technique to allow greater comparability. In some instances *a priori* information is known about all or a portion of such genes and in some embodiments  
10 *a priori* information about such genes is either not known or not considered in step 202. In some embodiments the molecular markers resulting from step are those molecular markers identified in Tables 1A through to 7I.

Measurement of molecular marker data of a plurality of the molecular markers in the blood of each member of training population 44 can be done using any known  
15 technique and preferably is done using large scale techniques which allow for the ability to obtain data for a large number of molecular markers and/or for a large number of individuals quickly and efficiently and at a relatively low cost. For example, microarray techniques and RT-PCR and/or Quantitative RT-PCR can be useful large scale techniques. For example, a high throughput or large scale technique is a technique which allows one to  
20 obtain data for large numbers of genes concurrently e.g. 1,000 genes, 5,000 genes, 10,000 genes, 15,000 genes 30,000 genes; or all of the genes of the genome of interest. It is expected that additional techniques are being developed and are also useful in embodiments of the invention to screen large numbers of genes quickly and efficiently.

Training population 44 includes a population of individuals made up of one or  
25 more trait subgroups with each individual in such trait subgroups having one or more traits.

In some embodiments, each trait subgroup represented in training population 44 includes molecular marker data from at least 3-4 different subjects. More preferably, each trait subgroup represented in training population 44 includes molecular marker data for at  
30 least ten different subjects. Still more preferably each trait subgroup represented in the training population 44 includes molecular marker data for at least 30, 40, 50, 100, 200, 500, 1000 or more subjects.

Each training population is selected to include two or more trait subgroups, each subgroup comprising trait subgroup members. Each of these two or more trait subgroups

differs with respect to a trait of interest and/or an aspect of a trait of interest. In one embodiment, the members of each of the trait subgroups have been diagnosed as having or not having the trait of interest by one or more known techniques. In another embodiment, the members of each trait subgroup are diagnosed for having or not having the trait of interest using a well accepted methodology for diagnosing of said trait.

For example, each member of a first trait subgroup of the training population has liver cancer, whereas each member of a second trait subgroup of the training population does not have liver cancer. In another embodiment, each member of a first trait subgroup of the training population has Alzheimer's, whereas each member of a second trait subgroup of the training population has manic depressive disorder, and each member of a third trait subgroup of the training population has schizophrenia, and each member of a fourth trait subgroup does not have any of the above conditions. In another example, the trait of interest is a disease such as prostate cancer, and the aspect of interest is the degree of advancement of the prostate cancer. Thus, each member of the first trait subgroup can be those subjects that have early stage prostate cancer, each member of a second trait subgroup can be those subjects that have later stage prostate cancer and each member of a third trait subgroup can be those subjects that do not have prostate cancer. In another example, the trait of interest is responsiveness of individuals having musculoskeletal disorders to a Cox 2 inhibitor. A first trait subgroup is comprised of individuals who are responsive to a treatment, a second trait subgroup is comprised of individuals who are responsive to treatment but demonstrate a toxic side-effect, and a third trait subgroup is comprised of individuals who are nonresponsive to treatment. In another embodiment, one trait subgroup can include those subjects that have not yet undergone treatment but who are later identified as being responders to treatment and a second trait subgroup can include those subjects that have not yet undergone treatment but who are later identified as non responders (*e.g.* demonstrates a toxic side-effect, demonstrates no improvement in condition, demonstrates a worsening of condition, *etc.*).

In some embodiments, members of each trait subgroup of the training population are preferably selected such that each trait subgroup of the training population has a similar distribution with respect to at least one, two, three, four, five, six, one or more, two or more, three or more, four or more, five or more, six or more, between one and 1000 other traits. For example, age, sex, body mass index (BMI), genetic variation information (*e.g.*, gene SNP mutations, restriction fragment length polymorphisms, microsatellite markers, restriction fragment length polymorphisms, and presence, absence or

characterization of short tandem repeats.), treatment regimens; co-morbidities; concentrations of metabolites, blood chemistry levels, and/or other indicators of health and/or wellness.

A treatment can include, but is not limited to, disease modifying treatments as well as treatments useful in mitigating the symptoms of disease and includes administration of one or more compounds, combinations of one or more compounds, application of a non-compound based therapeutic regimen, or any combination thereof where administration includes application of a single treatment, a regimen or course of treatment and the like. For example, treatments can include drugs specific for a disease such as drugs specific for Alzheimer's, cardiovascular disease, manic depression syndrome, schizophrenia, diabetes cancers including liver cancer, testicular cancer, bladder cancer, prostate cancer, kidney cancer, breast cancer, colon cancer, osteoarthritis, rheumatoid arthritis, osteoporosis, ankylosing spondylitis, or any other disease including those listed herein. . For example, treatments can include but are not limited to administration of VIOXX®, Celebrex®, non-steroidal anti-inflammatory drugs (NSAIDS), cortisone, visco supplement, Lipitor®, Adriamycin®, Cytosan®, Herceptin®, Nolvadex®, Avastin®, Erbitux®, Fluorouracil®, Largactil®, Sparine®, Vesprin®, Stelazine®, Fentazine®, Prolixin®, Compazine®, Tindal®, Modecate®, Moditen®, Mellarin, Serentil, Norvane, ®, Fluanxol®, Clopixol®, Taractan®, Depixol®, Clopixol®, Haldol®, Haldol®, Decanoate, Orap®, Inapsine®, Imap®, Semap®, Loxitane®, Daxol®, lithium, anticonvulsants (e.g., carbamazepine), antidepressants, and/or Moban®. More generally, a treatment can include any treatment or drug described in the *Compendium of Pharmaceuticals and Specialties*, Canadian Pharmaceutical Association; 26th edition, June, 1991; Krogh, *Compendium of Pharmaceuticals and Specialties*, Canadian Pharmaceutical Association; 27th edition, April, 1992. In another embodiment, a treatment can include administration of any compound described in the United States Food and Drug Administration list of approved drug products (the "Orange Book") that is found at <http://www.mco.edu/research/fda.html>.

In some embodiments, molecular marker data is not obtainable from each member of a training population or each member of a trait subgroup (for example, using microarray technology there may be an insufficient signal for one or more molecular markers for any particular member of the training population). Nevertheless, as would be understood by a person skilled in the art, candidate molecular markers can still be selected on the basis of the molecular marker data so long as data is obtainable for a sufficient number of molecular markers from a sufficient number of members of the training population. For

example, for each molecular marker, it is sufficient if data is available for at least 75%, 80%, 85%, 90% or 95% of the each trait subgroup of the training population.

Section 5.2 provides details on the types of blood samples from subjects in the training population that can be used to obtain data for molecular markers. Section 5.2 further provides details on how such blood samples can be obtained. Section 5.2 also provides details on the types of subjects that can be used to form training population 44 and the types of subpopulations that can be used in the training population.

Fig. 1 illustrates the data structure of a training population 44 in accordance with one embodiment of the present invention. There is a record 46 for each subject in training population 44. Each record 46 includes an optional subject identifier 48 for uniquely identifying the subject. Each record 46 includes a molecular marker data file 50 for storage of the molecular marker data measured in step 202. Fig. 4 provides more details on a molecular profile 50 resulting from Molecular Marker data processing module I in accordance with one embodiment of the present invention. The molecular profile 50 of Fig. 4 includes an identifier 302 for each molecular marker 302 tracked by profile 50. Then, for each respective molecular marker 302 in profile 50, there exists one or more measurements of molecular marker data 304. In some embodiments, more than one data point is measured for molecular markers 302. If more than one data point is measured for a molecular marker, then a statistical measure of central tendency (e.g. mean, median, average etc.) can be computed. Accordingly, such measurements for molecular marker data 304 can be stored in data structure 50.

There exists a trait characterization field 52 for each subject in training population 44. Preferably as many as possible traits of each member of training population 44 are documented in a trait characterization record (52). Documented traits include known condition or clinically measurable parameters; genetic likelihood of disease or condition; medications both past and current; environmental exposures, ethnicity, age, sex and the like. In some embodiments, training population 44 includes only two trait subgroups and trait characterization 52 is a binary choice between two values, where one value indicates that the corresponding subject belongs in a first trait subgroup and a second value indicates that the subject belongs in a second trait subgroup. In some embodiments, training population 44 is divided into a plurality of lists, where each list in the plurality of lists represents a different trait subgroup. In such embodiments, there is no need for a phenotypic characterization field 52.

Although not illustrated in Fig. 1, in some embodiments, there exists a scoring population in addition to the training population. The scoring population is used to evaluate each of the classifiers derived from the training population. The scoring population is made up of one or more individuals that have at least two trait subgroups in common with the training population. In some embodiments, multiple scoring populations are generated from the training population using one or more resampling or cross validation procedures including: bootstrapping; leave one out; leave n out; percent split and the like so as to evaluate the classifiers derived from the training population. In preferred embodiments, the members of the scoring population are not the members used in the training population.

In some embodiments, some aspects of step 202 are performed by first data molecular processing module I 54. As such, first data molecular processing module 54 can be a known software program, such as commercially available and/or academically available data processing programs.

*Step 204.*

In step 204, using the data measured in step 202, individual candidate molecular markers are identified, where the molecular marker data allows the differentiation as between two of the trait subgroups of the training population. In some embodiments, step 204 represents a series of pairwise comparisons, where each pairwise comparison is between molecular marker data for subjects from two different trait subgroups. In other words, data associated with molecular markers from a population of samples having one aspect of a trait of interest (a first trait subgroup) are compared with a population of samples having a second aspect of a trait of interest (a second trait subgroup) so as to identify molecular markers that are able to differentiate between the two trait subgroups (ie the molecular marker data enables the ability to differentiate between the two trait subgroups).

In instances where more than two trait subgroups are represented by a training population 44, more than two pairwise comparisons can be performed on the molecular marker data to identify lists of candidate molecular markers for each of the possible pairwise comparison.

A number of statistical techniques can be used to perform the pairwise comparisons of step 204. In some embodiments, standard statistical techniques such as a t-test are used. Methods based on conventional t-tests provide the probability ( $P$ ) that a difference in measured values for the data of a molecular marker between two different trait subgroups

occurs by chance. See, for example, Baldi *et al.*, 2001, Bioinformatics 17, pp. 509-519, 2001, which is hereby incorporated herein by reference in its entirety. The t-test compares the actual difference between two means in relation to the variation in the data (expressed as the standard deviation of the difference between the means). For instance, to determine  
5 whether a particular molecular marker discriminates between a first trait subgroup and a second trait subgroup, the mean of the data for the molecular marker in the first trait subgroup is compared to the mean of the data for the molecular marker in the second subgroup in accordance with the t-test. In some embodiments, the molecular marker data is such that it is deemed to discriminate between two trait subgroups when the t-test yields  
10 a score that matches or exceeds the  $p = 0.05$  level (95% confidence, “significant confidence”), the  $p = 0.01$  level (99% confidence, “highly significant confidence”) or  $p = 0.001$  (99.9% confidence, “very highly significant confidence”). In some embodiments, the t-test is applied with a Bonferroni correction or similar form of correction. In some embodiments, rather than using a t-test, nonparametric equivalents such as the Wald-  
15 Wolfowitz runs test, the Mann-Whitney U test, the Kolmogorov-Smirnov two-sample test or ROC are used.

In some embodiments, training population molecular marker data is obtained using a microarray and the Significant Analysis of Microarrays technique of Tusher *et al.* is used to identify molecular markers whose data discriminates between trait subgroups. See, for  
20 example, Tusher *et al.*, 2001, Proc. Natl. Acad. Sci. USA 98, 5116-5121. In some embodiments, Manduchis’ algorithms for assigning confidence to differentially expressed genes is used to identify molecular markers whose data discriminates trait subgroups. See, for example, Manduchi *et al.*, 2000, Bioinformatics 16, 685-598.

In some embodiments, there are a number of different trait subgroups represented  
25 within the training population. Thus, in such embodiments, application of a series of pairwise t-test can become computationally intensive and prone to underinclusiveness in the identification of discriminating molecular markers resulting for each binary comparison since the number of pairwise comparisons that must be performed grows quickly as a function of the number of trait subgroups present in training population 44.  
30 For example, if there are seven trait subgroups present in training population 44, a total of 21 pairwise (t-test class) test can be performed. In such embodiments, analysis of variance (ANOVA) can be used to simultaneously consider whether the data for a molecular marker produces statistically different means for each of the phenotypic data structures. ANOVA considers the data for a given molecular marker from each of the trait subgroups present in

training population 44 and produces a single number (the  $F$ -statistic) that can be evaluated for significance at any desired confidence value (e.g., the  $p = 0.05$  level, the  $p = 0.01$  level, the  $p = 0.001$  level, etc). ANOVA is described, for example, in Draghici, *Data Analysis Tools For DNA Microarrays*, 2003, Chapman & Hall, CRC Press, New York, pp. 155-187, which is hereby incorporated herein by reference in its entirety. In some embodiments, nonparametric equivalents to ANOVA, such as the *Kruskal-Wallis analysis of ranks* test, the Median test, Friedman's two-way analysis of variance, or the Cochran Q test, are used to identify molecular markers that have statistically different means as between two of the trait subgroups. In some embodiments, after running ANOVA, a means comparisons test such as Duncan's, Student-Newman-Keuls (SNK), Tukey-Kramer, Tukey's HSD, or Least Significant Difference (LSD) are run to determine which molecular markers have data that statistically differentiates as between one or more of the trait subgroups tested (e.g. has statistically different values in one or more of the trait subgroups tested). In some embodiments, such tests are performed instead of ANOVA or pairwise  $t$ -tests to identify molecular markers that discriminate two or more trait subgroups.

In some embodiments, a parametric test and a nonparametric test are run in step 204. If there are only two trait subgroups being compared (e.g., non-disease versus disease) then a Welch  $t$ -test (parametric test) and a Mann-Whitney test are used without multiple test corrections at decreasing  $p$ -values (e.g.,  $p < 0.05$ ,  $p < 0.01$ ,  $p < 0.005$ ,  $p < 0.001$ , etc.) until the number of candidate molecular markers is less than 50, less than 100, less than 150, less than 200, less than 250 etc.. If three or more trait subgroups are being compared, the Kruskal-Wallis (nonparametric) and Welch ANOVA (parametric) tests are used. Following the same procedure for instances where only two trait subgroups are being compared, additional molecular marker sets are produced in conjunction with multiple test corrections. An example of a test correction is the Benjamin-Hochberg false discovery rate. In some embodiments the post-hoc statistical tests for groups of three or more provided in GeneSpring version 6.1+ is used. The post-hoc test provides a means for determining which molecular markers are different between particular trait subgroups. Such post-hoc tests include the Student Newman Keuls test and the Tukey test.

In some embodiments, data for a test molecular marker from all possible trait subgroups in training population 44 is not used. Rather, similar to the case where pairwise  $t$ -tests are used, ANOVA is used to determine whether the data for a molecular marker can discriminate between some or all of the trait subgroups. For example, consider the case in which training population 44 includes five trait subgroups. In one approach, a pairwise  $t$ -

test can be used to identify molecular markers that statistically discriminate (e.g.  $p = 0.05$ ) between one of the possible pairs of trait subgroups in the training population. Similarly, ANOVA can be used to identify molecular markers that statistically discriminate between one of the possible triplets in the training population. Alternatively, ANOVA can be used to identify molecular markers that statistically discriminate between one of the possible quadruplets in the training population.

In some embodiments, either in addition to using statistical methods, or independently of statistical methods such as described herein, processing step 204 to select candidate molecular markers is done by looks for differential data abundances (e.g., differential expression). Such methods differ from those described above in the sense that variance as between the level of expression as between members of the same trait subgroup are not necessarily considered. In order to compare differential expression as between two or more trait subgroups, a statistical measure of central tendency (e.g. mean, median, average etc.) can be computed for each molecular marker within any trait subgroup. In some embodiments, the measure of differential data abundance (or differential expression) for a molecular marker product as between a first trait subgroup and a second trait subgroup is determined by measuring the fold change, for example a fold change of greater than 1.5, 2.0, 2.5, 3.0, 4.0 or higher can be selected.. In another embodiment, the measure of differential data abundance need not be quantified, but molecular markers products which on visual inspection display a clear difference in expression (ie abundance levels) as between two trait subgroups can be selected. To illustrate, consider a population  $P'$  that comprises trait subgroups "A" and "B". That is, each member of  $P'$  is classified into either subgroup "A" or "B" based on whether or not they exhibit or have a particular trait. In this situation, products of molecular markers that are present in large quantities/abundance in one group ("A" or "B") but not the other group are identified. For instance, molecular markers that strongly express in subgroup "A" but not in subgroup "B" can be identified from the measurements taken for each member of each subgroup in step 202. Likewise, molecular markers that express strongly in subgroup "B" but not subgroup "A" can be identified. These patterns of differential abundance of the products of the molecular markers can be used to identify candidate molecular markers. For an illustration of this approach, see Glob et al. 1999, Science 286: 531.

In embodiments where molecular markers are identified in select pairwise tests, such as pairwise  $t$ -tests or ANOVA tests of subsets of the total number of trait subgroups in training population 44, there might be several different lists of molecular markers. For



example, molecular marker list A might include molecular markers whose measured data (including normalized data etc.) discriminates between a first and second trait subgroup as determined by a first pairwise *t*-test. Molecular marker list B might include molecular markers whose data discriminates between a first and third trait subgroup as determined by a second pairwise *t*-test. Molecular marker list C might include molecular markers whose data discriminates between a first, second and third trait subgroup as determined by ANOVA. In some embodiments, each candidate molecular marker list 60 is preserved as an independent list in candidate molecular marker data structure 58 (Fig. 1).

In some embodiments, processing step 204 identifies a total of between 10 and 4000 candidate molecular markers for any particular training population. In other embodiments, step 204 identifies a total of between 500 and 2000 candidate molecular markers. In yet another embodiments, processing step 204 identified a total of between 100 and 1000 candidate molecular markers.

In some embodiments, some aspects of step 204 are performed by molecular marker candidate identification module 56A. Additionally, there exist known programs that can perform some of the functionality described in step 204. Such programs include those formerly sold by Silicon Genetics (e.g. GeneSpring™); now Agilent Technologies.

In some embodiments, candidate molecular markers identified using the above-described statistical or nonstatistical tests are clustered in order to visualize relationships between the genes. For example, in some embodiments GeneSpring™ is used to perform hierarchical clustering using the Spearman correlation statistic. In some embodiments, QT clustering is used to identify genes that have a similar pattern of expression across the specimens in training population 44. Clustering that can be employed in step 204 is described generally in Section 5.12. Further, Section 5.12 gives examples of some clustering techniques that can be used in step 204. Molecular markers for use in subsequent sections (e.g., for quantitative measurement using methods as described in step 206 below) can be ranked and selected by one or more criteria, including, but not limited to, fold change differences in molecular marker data between two or more trait subgroups, standard deviations of molecular marker data as between two or more trait subgroups using the above-described statistical tests, coefficient of variation, statistical significance (e.g., *p*-value from ANOVA and/or *t*-test, or other tests described above), level of expression as determined using molecular marker data, gene function, reproducibility of molecular marker data (includes intra- and inter-experimental), elucidated pathways / networks of the molecular markers as would be understood by a person skilled in the art (e.g. selecting a

molecular marker on the basis of an understanding of how said gene is known to function in the body) and the like. Thus in some embodiments, molecular markers for use in subsequent sections are chosen on the basis of the p value identified as a result of step 204 as a measure of the likelihood that the molecular marker data can distinguish as between the two trait subgroups and more particularly molecular markers are chosen wherein the p value is less than 0.5; less than 0.1, less than 0.05, less than 0.01, less than 0.005, less than 0.001, less than 0.0005, less than 0.0001, less than 0.00005, less than 0.00001, less than 0.000005, less than 0.000001 etc. In some embodiments, molecular markers for subsequent steps are chosen on the basis of the level of differential expression displayed by the molecular marker products as between the two or more trait subgroups. Note that in measuring differential fold change in blood, the fold change differences can be quite small, thus in some embodiments, selection of molecular markers is based on a differential fold change where the fold change is greater than 1.2, greater than 1.3, greater than 1.4, greater than 1.5, greater than 1.6, greater than 1.7, greater than 1.8, greater than 1.9, greater than 2.0, greater than 2.1, greater than 2.2, greater than 2.3, greater than 2.4, greater than 2.5, greater than 2.6, greater than 2.7, greater than 2.8, greater than 2.9, greater than 3.0, greater than 3.1, greater than 3.2, greater than 3.3, greater than 3.4 greater than 3.5, greater than 4.0 and the like. In some embodiments, it is helpful to select molecular markers on a basis of the combination of both p value and fold change as would be understood by a person skilled in the art. Thus in some embodiments, molecular markers are first selected as outlined above on the basis of the p value resulting from the molecular marker data and then a subselection of said molecular markers is chosen on the basis of the differential fold change determined from the molecular marker data. In other embodiments, molecular markers are first selected on the basis of differential fold change, and then subselection is made on the basis of p value. In some embodiments, the use of one or more of the selection criteria and subsequent ranking permits the selection of the top 2.5%, 5%, 7.5%, 10%, 12.5%, 15%, 17.5%, 20%, 30%, 40%, 50% or more of the ranked molecular markers for use in subsequent steps. In other embodiments, the selection criteria noted above can be set on the basis of the desired number of selected molecular markers for use in steps 206 and or other steps leading to the selection of the available set of markers for step 214. As would be understood, a selection criteria based on the desired number of selected molecular markers will depend upon the resources available for obtaining the molecular marker data for step 206 and/or the computer resources available for calculating and evaluating classifiers of all or a portion of possible combinations of the selected molecular

markers. In some embodiments, the desired number of selected molecular markers for use in step 214 can be 4,000; 3,000; 2,000; 1,000; 900; 800; 700; 600; 500; 400; 300; 200; 190; 180; 170; 160; 150; 140; 130; 120; 110; 100; 90; 80; 70; 60; 50; 40; 30; 20; 10. The more molecular markers which can be selected for use in step 214; the greater the  
5 likelihood of identifying classifier or classifiers which are particularly useful for diagnosis.

In some embodiments, one or more subjects of the training population are identified as outliers and are removed prior to identifying individual candidate molecular markers as described herein. These outlier members can then be removed from the training population prior to proceeding to later steps. As described herein, in one  
10 embodiment a neural network is used to identify such outliers. A neural network has a layered structure that includes, at a minimum, a layer of input units (and the bias) connected by a layer of weights to a layer of output units. Such units are also referred to as neurons. For output along a single dimension, the layer of output units includes just one output unit. However, neural networks can handle multiple quantitative responses (outputs  
15 along multiple dimensions) in a seamless fashion by providing multiple units in the layer of output units.

In multilayer neural networks, there are input units (input layer), hidden units (hidden layer), and output units (output layer). There is, furthermore, a single bias unit that is connected to each unit other than the input units. Neural networks are described in  
20 Duda *et al.*, 2001, *Pattern Classification*, Second Edition, John Wiley & Sons, Inc., New York; and Hastie *et al.*, 2001, *The Elements of Statistical Learning*, Springer-Verlag, New York.

The basic approach to the use of neural networks to identify outliers is to start with an untrained network. A training pattern is then presented to the untrained network. This  
25 training pattern comprises a training population and, for each respective member of the training population, an association of the respective member with a specific trait subgroup. Thus, the training pattern specifies measured molecular marker data from blood for molecular markers for each member of a training population as well as an indication as to which trait subgroup each member of the training population belongs. In preferred  
30 embodiments, training of the neural network is best achieved when the training population includes members from more than one trait subgroup.

In the training process, individual weights in the neural network are seeded with arbitrary weights and then the molecular marker data for each member of the training population is applied to the input layer. Signals are passed through the neural network and

the output determined. The output is used to adjust individual weights. A neural network trained in this fashion classifies each individual of the training population with respect to one of the input trait subgroups. In typical instances, the initial neural network does not correctly classify each member of the training population. Those individuals in the training population that are misclassified identify and determine an error or criterion function for the initial neural network. This error or criterion function is some scalar function of the trained neural network weights and is minimized when the network outputs match the desired outputs. In other words, the error or criterion function is minimized when the network correctly classifies each member of the training population into the correct trait subgroup. Thus, as part of the training process, the neural network weights are adjusted to reduce this measure of error. For regression, this error can be sum-of-squared errors. For classification, this error can be either squared error or cross-entropy (deviation). See, e.g. Hastie *et al.*, 2001, *The Elements of Statistical Learning*, Springer-Verlag, New York. Those individuals of the training population which are still incorrectly classified by the trained neural network, once training of the network has been completed, are identified as outliers and can be removed prior to proceeding.

In some embodiments, an ensemble of neural networks can be used on the training population and individuals ranked on the basis of the number of times an individual is misclassified by each neural network. In order to create the ensemble, each neural network can differ with respect to the initial seeded weighting. In another embodiment, each neural network can differ on the basis of randomly generated noise added to the molecular marker data for one or more molecular markers of each individual of the training population added to the input layer. In such an embodiment, this randomly generated noise can be applied by changing the amount of each of the measured molecular marker data of each member of the training population by a scaled random amount. When larger amounts of noise are required, the magnitude of the scaled random amount is increased. In any of these embodiments, the number of layers and the number of units in each layer can be adjusted in order to provide optimal results for any given set of conditions. In this manner, one can identify outliers which are misclassified in as many as 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more of the neural networks used.

#### *Step 205.*

Step 205 is optional. We have surprisingly found that certain molecular markers whose molecular marker data fails to discriminate individually as between two trait subgroups in step 204, are still more than incrementally useful when utilized in

combinations with other candidate molecular markers selected in step 204. In particular we have been able to identify molecular markers whose data fails to individually discriminate as between two trait subgroups in the pairwise comparison of step 204 but contribute to a classifier identified in step 216 from a combination which includes one or more candidate molecular markers identified in step 204 (“combination friendly molecular markers”). Thus, in order to ensure that molecular markers which may be useful in combinations are not removed prematurely, optional step 205 is performed.

In step 205, all or a portion of the molecular markers for which data has been or can be obtained in at least two of the trait subgroups of the training population are utilized (“putative combination molecular markers”). For purposes of step 205, in one embodiment, the data is obtained using a technique which allows for fast and efficient data generation for all of the molecular markers of the genome of interest chosen. In another embodiment the data is obtained using one or more of the techniques as described in Section 5.3 and/or 5.4. In another embodiment, the data is obtained using microarray technology. In a preferred embodiment, the data used is the data obtained for step 202

In order to identify additional candidate molecular markers, combinations of molecular markers are chosen and a mathematical model applied to the molecular marker data for each molecular marker of the combination resulting in a classifier for each combination. The mathematical model applied can be selected from those defined in Section 5.14. In some embodiments, each possible combination of 2, and/or 3, and/or 4, and/or 5, and/or 6, and/or 7, and/or 8, and/or 9 and/or 10 or more of the putative combination friendly molecular markers are tested. For example, if there are 8,000 putative combination friendly molecular markers, each possible combination of 8 or less molecular markers can be written as follows:

$$\frac{8,000!}{((8,000 - 8)! (8)!)}$$

Each classifier resulting from each combination is scored as described more fully in step 220. In some embodiments, the classifiers are scored using the training population so as to permit time and cost savings. In other embodiments, the classifiers are scored using a scoring population. In yet other embodiments, the classifiers are scored using other resampling or cross validation procedures so as to generate multiple scoring populations. Having scored the classifiers, a subset of classifiers are then selected based on the score.

In some embodiments, the subset of classifiers is any number less than the total number of combinations evaluated. In some embodiments, the top 10%, top 20%, top 30%, top 40%, or top 50% of the classifiers generated are chosen. In some embodiments,

wherein scoring is done using ROC area under the curve, those classifiers with an ROC area under the curve of 0.5, 0.6, 0.7, 0.8, 0.9 or 1.0 are selected.

Having selected a number of classifiers, each representing a combination of molecular markers, the number of occurrences of each putative combination friendly molecular marker in the combinations of the selected classifiers are determined. Putative combination friendly molecular markers can then be selected as combination friendly molecular markers so as to used as candidate molecular markers based on the number of reoccurrences of said molecular marker in the selection of combinations evaluated. In one embodiment, 5, 10, 15, 20, 30, 50, 100, 150, 200 or more additional candidate molecular markers not previously selected in step 204 are chosen to proceed to step 206. In other embodiments, the top 10%, top 20%, top 30%, top 40%, or top 50% of combination friendly molecular markers as determined by reoccurrence statistics are selected to be included in the selected set of candidate molecular markers for purposes of choosing combinations to create classifiers in accordance with steps 214 to 218.

*Step 206.*

In step 206, second molecular marker data is obtained for the candidate molecular markers identified in step 204. In one embodiment, the second molecular marker data is measured using any technique described in Section 5.3 or 5.4 or equivalents thereof. In another embodiment, the same technique used to measure the first molecular marker data in step 202 is used to obtain the second molecular marker data. In other embodiments, an alternative technique is used to measure the second molecular marker data. In other embodiments, the first molecular marker data is obtained using one of the following techniques: microarray, and/or RT-PCR and the second molecular marker data is obtained using any technique but microarray. In other embodiments, the first molecular marker data is obtained using microarray and the second molecular marker data is obtained using any technique except for microarray. The use of second molecular marker data is preferred because the changes in differential expression or abundance of the product of the molecular marker in blood as between trait subgroups can be as low as a 1.1 fold, 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold etc. which makes less sensitive and reproducible techniques less reliable. In addition, techniques which are preferable for the data collection to allow large scale screening in step 202 such as microarray have been shown to have significant inherent reproducibility issues with high standard deviation as between experiments. As such it is necessary to obtain second molecular marker data so as to ensure the accuracy of the ultimate classifiers identified.

Techniques utilized to obtaining second molecular marker data for the plurality of molecular marker products are those techniques known to measure abundance of RNA and/or protein including the techniques described in Section 5.3 and 5.4.

5 In some embodiments, it is helpful to obtain a third series of molecular marker data (ie third molecular marker data, fourth molecular marker data etc.) which can be molecular marker data of the training population used in steps 202 or of a different training or scoring population using any known technique including those techniques described in sections 5.3 and 5.4. Preferably more expensive and/or time consuming techniques are used once smaller numbers of candidate molecular markers have been identified

10 In some embodiments, some aspects of step 206 are performed by molecular marker data processing module II - 61. The exact nature of the functionality of molecular processing module 61 will depend on the type of measurement assay used in step 206. However, it is contemplated that module 61 will be used to record measurement values for molecular marker data in a profile similar to molecular marker data processing module I -  
15 50, perform any necessary error correction techniques, normalization techniques (*e.g.*, techniques described in Bevington and Robinson, *Data Reduction and Error Analysis for the Physical Sciences*, Second Edition, WCB/ McGraw-Hill, 1992, *etc.*) and/or perform any measurement techniques that can be coded in a digital computer .

*Step 208.*

20 Step 208 is optional and allows for the selection of individual candidate molecular markers of step 206 which can be removed prior to the process of selecting and evaluating combinations of molecular markers in steps 214/216. In optional step 208, one or more candidate molecular markers in data structure 58 (Fig. 1) are eliminated. In optional step 208, the same types of tests that were performed in step 204 can be performed. The main  
25 difference is that in step 208, the quantitative data measured in step 206 using low throughput methods is used whereas in step 204, the high throughput data measured in step 202 is used. Data measured in step 206 is used in step 208 to validate the candidate molecular markers.

30 In one specific embodiment, training population 44 consists of a first trait subgroup and a second trait subgroup and step 208 comprises performing a t-test or a nonparametric equivalent of the t-test on each candidate molecular marker using the molecular marker data measured in step 206 to verify for each candidate molecular marker that the molecular marker data differentiates between the first trait subgroup and the second trait subgroup with some measure of statistical confidence. Candidate molecular markers whose

molecular marker data are less effective in differentiating between the two trait subgroups (e.g. have a p value that is greater than .05) are removed from data structure 58 and are no longer considered as candidate molecular markers.

In another specific embodiment, training population 44 consists of a first trait subgroup, a second trait subgroup, and a third trait subgroup. In this specific embodiment, ANOVA or a nonparametric equivalent is performed independently on each candidate molecular marker in data structure 58 to verify that each molecular marker differentiates between the three subgroups using the molecular marker data. Candidate molecular markers whose molecular marker data are less effective in differentiating between the three trait subgroups (e.g. have a p value that is greater than .05) are removed from data structure 58 and are no longer considered as candidate molecular markers.

In some embodiments, each molecular marker is validated by using the data for each molecular marker to generate a Receiver Operating Characteristic (ROC) curve.

ROC curves are generally discussed in Park et al., Korean J. Radiol. 5, p. 11, which is hereby incorporated herein by reference in its entirety. In one embodiment of the present invention, an ROC curve is computed for each candidate molecular marker in training population 44 using the molecular marker data measured in step 206. As noted in step 202, training population 44 includes, for each specimen in the training population, an indication 52 as to whether or not the specimen has a particular trait under study.

Each respective ROC curve graphs the True Positive Fraction (TPF) as compared with 1/ the False Positive Fraction (FPF). For example, consider the case in which molecular marker A is being validated and the data for molecular marker A that was measured in step 206 is expression level of the molecular marker A in blood samples from subjects. Table B provides hypothetical values for the abundance of A across training population 44.

Table B: Values for molecular marker data of A across training set 44.

[A]	Presence / Absence of Disease
453	Y
437	Y
424	Y
374	Y
202	N
158	Y
102	N
37	N
0.54	N



In Table B, each line represents a different specimen in the training population. If the relationship between [A] (data of cellular constituent A) and the presence of disease in subjects in the training population is statistically very significant, all positive results (where specimens have the disease) would be at the top of Table B and all negative results (where biological specimens do not have the disease) at the bottom of the Table B.

To plot the ROC curve corresponding to the test illustrated in Table B, the table is divided into a number of cutoff levels. Then, the sensitivity (TPF) and specificity (TNF) of each cutoff level is computed. Sensitivity and specificity are defined with reference to the decision matrix of Table C.

Table C: Decision matrix.

Test result	True Feature Status		
	Positive	Negative	Total
Positive	TP	FP	T+
Negative	FN	TN	T-
Total	D+	D-	

In Table C, TP means the number of true positives, FP means the number of false positives, FN means the number of false negatives, and TN means the number of true negatives.

Sensitivity is the proportion of subject with a trait (*e.g.*, a disease or particular biological phenotype) who test positive for the feature. In probability notation sensitivity is  $P(T^+|D^+) = TP / (TP+FN)$ . Specificity is the proportion of patients without the trait who test negative for the feature. In probability notation specificity is  $P(T^-|D^-) = TN / (TN + FP)$ .

The ROC curve is defined as a plot of the sensitivity as the y-coordinate versus 1-specificity (false positive rate) as the x-coordinate. Thus, for Table B, where each line of the Table B represents an independent cutoff level, the following ROC data points are derived.

Table D: ROC data points for Table B.

Ratio Cutoff Level	Sensitivity	1-Specificity
No row	0	0
First row	0.2	0
First two rows	0.4	0
First three rows	0.6	0
First four rows	0.8	0

Ratio Cutoff Level	Sensitivity	1-Specificity
First five rows	0.8	0.25
First six rows	1	0.25
First seven rows	1	0.5
First eight rows	1	0.75
First nine rows	1	1

To compute the last row of Table D, the number of TP, FP, FN, and TN are counted in Table B when the condition is imposed that the classifier predicts that no specimen in Table B is positive for presence of the trait (e.g., disease or a particular biological phenotype). This, of course, is not an accurate classifier as reflected in the respective sensitivity and specificity values of 0 and 1. Plotting sensitivity by 1-specificity yields the coordinate (0,0) as illustrated in the last row of Table D. Figure 7 illustrates the ROC curve based upon the data points illustrated in Table D. As illustrated in Fig. 7, a ROC curve begins at coordinate (0,0) and ends at coordinate (1,1).

Once an ROC curve has been computed for a molecular marker, in one embodiment, the area under the ROC curve can be quantified. Generally, an area of 1.0 represents a molecular marker that is a perfect diagnostic indicator of the presence of absence of the trait. Preferably an area of greater than 0.5 is desired for a diagnostic indicator, but it will depend upon the trait of interest. For example measurement of protein PSA levels currently used to diagnose prostate cancer has an ROC of 0.47.

In some embodiments there are as many as fifty candidate molecular markers in data structure 58 at this stage of the inventive method. In some embodiments there are more than fifty candidate molecular markers. In practice, the number of candidate molecular markers that remain can be set to any desired number by raising or lowering the criteria for eliminating molecular markers. For example, smaller p values from ANOVA or t-tests, or larger ROC curve areas can be required if the total number of molecular markers is too large.

#### *Steps 210 and 212.*

Step 210 is optional and allows the additional removal of individual candidate molecular markers of step 206 by evaluating how each individual candidate molecular marker performs within a model which evaluates a combination of molecular markers prior to performing the evaluation of combinations in step 214/216.

In optional step 210 all or a portion of the remaining candidate molecular markers in data structure 58 are used to generate a regression classifier. To compute the regression classifier, measured data from step 206 for the molecular markers in two different trait

subgroups in training population 44 are used. In some embodiments, the two different trait subgroups respectively represent a diseased and nondiseased state. In some embodiments, the two different trait subgroups respectively represent a first diseased state (e.g. cancer) and a second unrelated diseased state (e.g., Alzheimer's disease). In some embodiments, the two different trait subgroups represent those subjects that are responsive to drug therapy and those subjects that are not responsive to drug therapy. In still other embodiments, the two different trait subgroups from which molecular marker data is obtained represent data from subjects obtained *a priori* to treatment, but that have been classified into different trait subgroups on the basis of the ultimate response to treatment. In some embodiments, the two different trait subgroups respectfully represent two different stages of a disease (e.g., moderate versus advanced).

In some embodiments, data for between ten and thirty candidate molecular markers in the two select trait subgroups is used in the logistic regression. In some embodiments, between twenty and one hundred candidate molecular makers in the two select trait subgroups is used in the logistic regression. In still other embodiments, all the candidate molecular markers in the two select trait subgroups are used in the logistic regression.

In step 210 logistic regression can be used because one of the dependent variables is binary - absence or presence of a particular phenotype. For example, consider the case in which molecular marker data from a first trait subgroup and molecular marker data from a second trait subgroup is used in step 210. The first trait subgroup is characterized by a first disease and the second trait subgroup is characterized by a second disease. In such instances, what can be considered by logistic regression is absence or presence of the first disease in subjects. Alternatively, what can be considered by logistic regression is absence or presence of the second disease in subjects.

In general, the multiple regression equation of interest can be written

$$Y = \alpha + \beta_1 X_1 + \beta_2 X_2 + \dots + \beta_k X_k + \varepsilon$$

where  $Y$ , the dependent variable, is presence (when  $Y$  is positive) or absence (when  $Y$  is negative) of the trait (e.g., phenotype, condition) associated with the first trait subgroup considered in step 204. This classifier says that the dependent variable  $Y$  depends on  $k$  explanatory variables (the measured data values for the  $k$  candidate molecular markers from subjects in the first and second trait subgroups in training population 44), plus an error term that encompasses various unspecified omitted factors. In the above-identified classifier, the parameter  $\beta_1$  gauges the effect of the first explanatory variable  $X_1$  on the

dependent variable  $Y$ , holding the other explanatory variables constant. Similarly,  $\beta_2$  gives the effect of the explanatory variable  $X_2$  on  $Y$ , holding the remaining explanatory variables constant.

In general, in the multiple regression procedure, estimates for  $\beta_i$  are obtained by taking into account how uncontrolled changes in other variables influence  $Y$ . Thus, in specific embodiments of the present invention, regression is used to eliminate at least some of the candidate molecular markers rather than relying entirely on the tests described in step 208 because the regression takes into account patterns in which multiple molecular markers influence the dependent variable (absence or presence of a trait) in a concerted fashion.

Because the dependent variable data is binary, logistic regression can be used. The logistic regression classifier is a non-linear transformation of the linear regression. The logistic regression classifier is termed the "logit" classifier and can be expressed as

$$\ln[p/(1-p)] = \alpha + \beta_1 X_1 + \beta_2 X_2 + \dots + \beta_k X_k + \varepsilon \quad \text{or}$$

$$[p/(1-p)] = \exp^\alpha \exp^{\beta_1 X_1} \exp^{\beta_2 X_2} \times \dots \times \exp^{\beta_k X_k} \exp^\varepsilon$$

where,

$\ln$  is the natural logarithm,  $\log_e$ , where  $e=2.71828\dots$ ,

$p$  is the probability that the event  $Y$  occurs,  $p(Y=1)$ ,

$(1-p)$ , the probability that the event  $Y$  does not occur,  $p(Y \neq 0)$ ,

$p/(1-p)$  is the "odds ratio",

$\ln[p/(1-p)]$  is the log odds ratio, or "logit", and

all other components of the classifier are the same as the general regression equation described above. It will be appreciated by those of skill in the art that the term for  $\alpha$  and  $\varepsilon$  can be folded into a single constant. Indeed, in preferred embodiments, a single term is used to represent  $\alpha$  and  $\varepsilon$ . The "logistic" distribution is an S-shaped distribution function. The logit distribution constrains the estimated probabilities ( $p$ ) to lie between 0 and 1.

In some embodiments of the present invention, the logistic regression classifier is fit by maximum likelihood estimation (MLE). In other words, the coefficients (e.g.,  $\alpha$ ,  $\beta_1$ ,  $\beta_2$ , ...) are determined by maximum likelihood. A likelihood is a conditional probability (e.g.,  $P(Y|X)$ , the probability of  $Y$  given  $X$ ). The likelihood function ( $L$ ) measures the

probability of observing the particular set of dependent variable values ( $Y_1, Y_2, \dots, Y_n$ ) that occur in the sample data set. It is written as the probability of the product of the dependent variables:

$$L = \text{Prob}(Y_1 * Y_2 *** Y_n)$$

5 The higher the likelihood function, the higher the probability of observing the  $Y$ s in the sample. MLE involves finding the coefficients ( $\alpha, \beta_1, \beta_2, \dots$ ) that makes the log of the likelihood function ( $LL < 0$ ) as large as possible or -2 times the log of the likelihood function (-2LL) as small as possible. In MLE, some initial estimates of the parameters  $\alpha, \beta_1, \beta_2, \dots$  are made. Then the likelihood of the data given these parameter estimates is  
10 computed. The parameter estimates are improved the likelihood of the data is recalculated. This process is repeated until the parameter estimates do not change much (for example, a change of less than .01 or .001 in the probability). Examples of logistic regression and fitting logistic regression classifiers are found in Hastie, *The Elements of Statistical Learning*, Springer, New York, 2001, pp. 95-100, which is hereby incorporated by  
15 reference in its entirety.

*Step 212.*

In specific embodiments, all or a portion of the candidate molecular markers are used and the molecular marker data fit using logistic regression. Then, in a stepwise fashion, some of the molecular markers are eliminated from the classifier using backward  
20 stepwise regression. Backward stepwise regression begins with a full or saturated classifier and variables are eliminated from the classifier in an iterative process. The fit of the classifier is tested after the elimination of each variable (molecular marker) to ensure that the classifier still adequately fits the molecular marker data. When no more variables can be eliminated from the classifier or a desired number of molecular markers remain in  
25 the classifier, the analysis has been completed. In specific embodiments, the regression applied in step 210 is used to refine the candidate molecular marker list to less than 25, less than 24, less than 23, less than 22, less than 21, or less than 20 molecular markers.

In one embodiment, a logistic regression classifier is computed using all or a portion of the available candidate molecular markers in data structure 58. Then,  
30 coefficients are tested for significance for inclusion or elimination from the classifier using a Wald test, a likelihood-ratio test (chi-squared statistic), a Hosmer-Lemshow Goodness of Fit Test, or the like. For example, the likelihood-ratio test uses the ratio of the maximized value of the likelihood function for the full classifier ( $L_1$ ) over the maximized value of the

likelihood function for the simpler classifier ( $L_0$ ) in which one or more molecular markers have been removed. The likelihood-ratio test statistic equals:

$$-2\log\left(\frac{L_0}{L_1}\right)$$

This log transformation of the likelihood functions yields a chi-squared statistic.

5        *Step 213.*

Step 213 is optional. We have found that performing optional step 213 provides a significant improvement in identifying classifiers which are particularly useful in diagnosis of a disease or condition of interest. In optional step 213, clinically measurable parameters are identified which are thought to be relevant to the trait of interest for which a classifier  
10 is desired. For example, where the trait of interest is prostate cancer, clinically measurable parameters chosen are those that are known or are shown to be relevant to the trait of interest. For example in one embodiment, clinically measurable parameters relevant to prostate cancer can include age of subject, level of prostate specific antigen (PSA); and volume of prostate. In yet another embodiment, where the trait of interest is osteoarthritis,  
15 some relevant clinically measurable parameters are age and body mass index (BMI). The selected clinically measurable parameters are then included as part of the “selected set of candidate molecular markers” and are treated as molecular markers for the purpose of selecting combinations and developing classifiers in step 214 through 218 as described below.

20        In order to treat the clinically measurable parameter as a molecular marker for purposes of step 214 through 218, the clinically measurable parameter must have associated data. In some embodiments, where the clinically measurable parameter is one which has an associated value – for example age, blood glucose level, PSA level, blood pressure, body mass index, etc., the value can be treated as the molecular marker data for  
25 purposes of steps 214 through 218. In some embodiments there is no value associated with the clinically measurable parameter, for example where the relevant clinical parameter is determinable but does not provide a value. In those cases, a value can be assigned to represent each aspect of the clinically measurable parameter. For example where the sex of a person is the clinically measurable parameter, a value of 1 can be  
30 assigned to represent that the person is male, and a value of 0 can be assigned to represent that the person is female. As yet another example, where the relevant clinically measurable parameter is ethnicity, a different value can be assigned to each ethnicity (e.g.

1 caucasian, 2 asian, 3ashkanazi jew etc. and said value can be used as the molecular marker data associated with ethnicity for purposes of step 214 through 218.

*Step 214.*

Steps 214 through 218 provide an approach in which all or a portion of the possible combinations of the selected set of candidate molecular markers resulting from steps 202-213 are chosen. Molecular marker data from each candidate molecular marker in a elected combination is applied to a mathematical model as described more fully in Section 5.14. If there are N selected molecular markers at this stage then, in some embodiments, as many as 2N-1 different combinations can be selected and classifiers can be computed for each of these combinations. For example, consider the case in which three molecular markers are selected after any combination of steps 201 through 212 have been performed and logistic regression is used in step 216. In this case, the following 23-1 mathematical models can be used to form 23-1 corresponding classifiers:

$$\ln[p/(1-p)] = \alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \varepsilon$$

$$\ln[p/(1-p)] = \alpha + \beta_1 X_1 + \beta_2 X_2 + \varepsilon ,$$

$$\ln[p/(1-p)] = \alpha + \beta_1 X_1 + \beta_3 X_3 + \varepsilon ,$$

$$\ln[p/(1-p)] = \alpha + \beta_2 X_2 + \beta_3 X_3 + \varepsilon ,$$

$$\ln[p/(1-p)] = \alpha + \beta_1 X_1 + \varepsilon ,$$

$$\ln[p/(1-p)] = \alpha + \beta_2 X_2 + \varepsilon , \text{ and}$$

$$\ln[p/(1-p)] = \alpha + \beta_3 X_3 + \varepsilon .$$

In these mathematical models,  $\alpha$ ,  $\beta_1$ ,  $\beta_2$ , ...,  $\beta_N$  represent coefficients that are regressed against molecular marker data whereas  $X_1$ ,  $X_2$ , ...,  $X^N$  each represent a different RNA or protein (or more generally, a molecular marker) for which molecular marker data is available. In some embodiments any one of elements  $X_1$ ,  $X_2$ , ...,  $X^N$  can represent a clinically measurable parameters. In a preferred embodiment for each combination chosen, at least one of the molecular markers of the series of  $X_1$ ,  $X_2$ , ...,  $X^N$  does not represent a clinically measurable parameter. In some embodiments, additional interaction

terms are also considered, producing non linear behaviour and resulting in greater than or less than as  $2^{N-1}$  different combinations. In some embodiments, additional interaction terms are also considered, producing non linear behaviour. For instance, in the example above, another mathematical model to which molecular marker data can be applied in order to form a classifier is:

$$\ln[p/(1-p)] = \alpha + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_2 X_3 + \varepsilon$$

where the coefficient  $\beta_4$  represents the interaction between molecular marker  $X_2$  and  $X_3$ . In such embodiments, more than  $2^N - 1$  "combinations" and thus more than  $2^N - 1$  classifiers are considered. In addition to the possibility of interaction terms, the present invention encompasses nonlinear variables. Examples of nonlinear variables include variables that are squared, squared rooted, or in fact, taken to any power. For instance, additional examples of mathematical models to which molecular marker data can be applied include:

$$\ln[p/(1-p)] = \alpha + \beta_2 (X_2)^2 + \beta_3 X_3 + \beta_4 X_2 X_3 + \varepsilon$$

$$\ln[p/(1-p)] = \alpha + \beta_2 (X_2)^{1/2} + \beta_3 X_3 + \beta_4 X_2 X_3 + \varepsilon$$

In some embodiments, a logarithmic or exponential function is applied to one or more of the variables. In some embodiments, ratios of molecular marker data can be used as a mathematical model. For example, consider the case in which regression is used to apply molecular marker data to the following equation in order to develop a classifier:

$$\ln[p/(1-p)] = \alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \varepsilon$$

Above, it was noted that  $X_1, X_2, \dots, X_N$  each represent the product of a different gene (or more generally, a molecular marker or molecular marker like element) for which molecular marker data is available. However, in the case where ratios are selected for use in mathematical models which are subsequently scored, each  $X_1, X_2, \dots, X_N$  can in fact represent a ratio of abundance and/or expression levels for two different molecular marker products e.g. RNA or proteins, or any other type of molecular marker. For example,  $X_1$  can represent the ratio between molecular marker data measured in step 206 representative of gene (molecular marker) A and data for gene B in training population 44. Mixed forms of mathematical models are also possible. For example, some variables  $X$  can represent ratios between the molecular marker data of two molecular markers whereas other variables  $X$  can represent molecular marker data of discrete molecular markers as opposed to ratios of molecular marker data. In one specific embodiment a "ratio" of the RNA products of two molecular markers can be used and all or some of the possible combinations of said "ratios" can be utilized. For example, where the molecular marker



data is a measure of abundance of RNA is determined using quantitative RT-PCR, the measure of the expression level of gene (molecular marker) A and the measure of the expression level of gene B can be used as a single term. In some embodiments this is done by first determining the level of expression of each gene individually as compared with an internal housekeeping control such as  $\beta$ -actin:

e.g.  $\Delta Ct = Ct_{\text{gene A}} - Ct_{\beta\text{actin}}$

where  $Ct_{\text{gene A}}$  is the threshold cycle of amplification of GeneA and  $Ct_{\beta\text{actin}}$  is the threshold cycle of amplification of the internal control  $\beta$ -actin. Similarly the level of expression of gene B is also determined in comparison with an internal housekeeping control

e.g.  $\Delta Ct = Ct_{\text{gene B}} - Ct_{\beta\text{actin}}$

In order to combine the terms into a single term for purposes of creating a classifier using “ratios” of the two terms - the terms are combined as follows to form a single variable (e.g. X).

$\Delta Ct = Ct_{\text{gene A}} - Ct_{\text{gene B}}$

This is commonly described as the use of ratios given the logarithmic nature of the measure of Ct. Thus in some embodiments, the  $X_1, X_2, \dots, X_N$  of a classifier, each term represents the “ratio” of two molecular markers. In other embodiments the Ct scores are compared directly rather than compared with an internal control.

For example, consider the case in which the desire is to form a classifier that discriminates between a first trait subgroup and a second trait subgroup wherein each term of the classifier represents molecular marker data which is derived from a combination of molecular markers using ratios as outlined above (e.g.  $\Delta Ct = Ct_{\text{gene A}} - Ct_{\text{gene B}}$ ). In such a case, each variable actually represents two molecular markers – the ratio of the molecular marker data for two molecular markers. Therefore in instances, for example, where 10 molecular markers have been identified by the funneling process of steps 202-210, 45 possible combinations of “ratios” of molecular markers can be formed

e.g.  $\frac{n!}{(n-2)!2!}$

where n is the number of possible molecular markers (e.g. 10).

In some embodiments it is particularly useful to select molecular markers where the molecular marker data will work well in the form of a “ratio” thus, as part of step 214, in one embodiment, prior to selecting combinations of molecular markers, molecular markers whose molecular marker data can be combined as ratios are first identified.

The use of molecular marker data as variables in which the variable representing the product of the molecular marker is in the form of ratios or raised to some arbitrary power (*e.g.*,  $\alpha$ , 2, N, *etc.*) is not limited to mathematical models based on regression. Such variables can be used in any of the mathematical models described herein (*e.g.*, neural networks). For example, consider the case in which the desire is to form a classifier that discriminates between a first trait subgroup and a second trait subgroup wherein each term of the classifier is a combination of molecular markers evaluated as a ratio. In step 214, in one embodiment, prior to selecting ratios of molecular markers, molecular markers which can be combined as ratios are first identified. Molecular markers which can be combined as ratios are those molecular markers wherein the ratio as between said molecular markers is a value which is not equal to 1.0 (or in one embodiment wherein  $\Delta Ct = Ct_{\text{gene A}} - Ct_{\text{gene B}}$  does not equal zero. In one embodiment, a first set of molecular markers and a second set of molecular markers are selected to create ratios such that the first set of molecular marker data demonstrates the molecular marker is upregulated in the first trait subgroup (relative to the second trait subgroup) in training population 44 and a second set of molecular marker data demonstrates that the molecular marker is downregulated in the first trait subgroup in training population 44 (relative to the second trait subgroup). Thus, for example an upregulated gene is one in which  $\Delta Ct = Ct_{\text{gene B}} - Ct_{\beta\text{actin}} > 0$  and a downregulated gene is one in which  $\Delta Ct = Ct_{\text{gene A}} - Ct_{\beta\text{actin}} < 0$ ,

Here, the term upregulated or downregulated generally means that such up or down regulation is observed in the training population with some measure of statistical confidence, for example a *t*-test having a *p* value of 0.05, less than 0.01, less than 0.005, less than 0.001, less than 0.0005, less than 0.0001, less than 0.00005, less than 0.00001, or less. Then, ratios of molecular markers can be formed using one molecular marker from the first set and a second molecular marker from the second set.

In another embodiment, a ratio for use in a selected combination is one in which the numerator represents the molecular marker data that demonstrates the molecular marker is upregulated in a first trait subgroup (as compared with a second trait subgroup) and the denominator represents the molecular marker data that demonstrates the molecular marker is upregulated in a second trait subgroup (as compared with a first trait subgroup). With such a ratio, a value greater than "1" indicates that the organism from which the molecular marker data was measured is a member of the first trait subgroup whereas a value less than "1" indicates that this organism is a member of the second trait subgroup. Thus, in some embodiments, step 214 comprises obtaining combinations of ratios of

molecular marker data. In some embodiments, step 214 comprises obtaining some multiple of molecular markers and forming a plurality of ratios of the molecular marker data so as to generate a plurality of combinations of molecular markers.

In step 214, a combination of molecular markers is selected. In some  
5   embodiments, this combination of molecular markers consists of a single molecular  
marker. In some embodiments, this combination of molecular markers comprises 2, 3, 4,  
5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, as many as 30, as many as 40, as  
many as 50 or more molecular markers. In some embodiments, this combination of  
molecular markers consists of a combination of ratios of molecular markers wherein the  
10   combination comprises 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, as  
many as 30, as many as 40, as many as 50 or more molecular markers. For each candidate  
molecular marker added, the number of possible combinations grows exponentially. The  
limitation to the number of combinations selected for evaluation is dependent upon the  
capacity of the computer, network of computers or supercomputers utilized. In one  
15   embodiment, all possible combinations of molecular markers resulting from steps 202-213  
(or resulting from some subset of steps 202-213) are chosen. In another embodiment, all  
possible combinations of ratios of molecular markers resulting from steps 202-213 (or  
resulting from some subset of steps 202-213) are chosen. In another embodiment, one can  
subject all possible pairs of candidate molecular markers; all possible combinations of  
20   three molecular markers, all possible combinations of four molecular markers; all possible  
combinations of five molecular markers, all possible combinations of six molecular  
markers, all possible combinations of seven molecular markers etc. In another  
embodiment, all possible combinations of two sets of ratios are chosen, in another  
embodiment, all possible combinations of three sets of ratios are chosen, in another  
25   embodiment, all possible combinations of four sets of ratios are chosen, in another  
embodiment, all possible combinations of five sets of ratios are chosen. Each of the  
combinations of molecular markers is evaluated in subsequent processing steps.

*Step 216.*

In step 216, a classifier is computed using each combination of molecular markers  
30   chosen in the last instance of step 214 and by applying the classifier to the molecular  
marker data measured for each molecular marker of this combination of molecular markers  
to a mathematical model, such as the mathematical models defined in Section 5.14  
resulting in one or more classifiers for each combination. As described more thoroughly in  
Step 204, in some embodiments, one or more subjects of the training population are

identified as outliers and are removed prior to computing classifiers for each combination of molecular markers chosen.

In order to compute a classifier, in some embodiments, the mathematical model is a regression model, a neural network, a clustering model, principal component analysis, nearest neighbor classifier analysis, linear discriminant analysis, quadratic discriminant analysis, a support vector machine, a decision tree, a genetic algorithm, classifier optimization using bagging, classifier optimization using boosting, classifier optimization using the Random Subspace Method, Bayesian Networks (see F. V. Jensen. "Bayesian Networks and Decision Graphs". Springer. 2001, which is incorporated herein by reference in its entirety), a projection pursuit, weighted voting, a ratio or combination of ratios, or any combination of the above. Representative mathematical models that can be used in the present invention are described in Section 5.14. In the case where the mathematical model is a ratio or combination of ratios, steps 214 and 216 involve using the low throughput molecular marker data from training population 44 that was measured in step 206 to determine which molecular markers should be in the numerator of the ratios and which molecular markers should be in the denominator of the ratios. In some embodiments, the mathematical model used comprises a plurality of ratios of the molecular marker data. In such embodiments, the molecular marker data used in the numerators of the plurality of ratios can be the same or different than the molecular marker data used in the denominators of the plurality of ratios. In other words, a given molecular marker can be represented in the numerator of more than one ratio in the plurality of ratios or represented in the denominator of more than one ratio in the plurality of ratios.

*Step 218.*

In optional step 218 a determination is made as to whether all of the possible desired combinations of molecular markers to be tested have been considered. As discussed above in step 214, all or a portion of possible combinations may be tested. If not (218-No) process control returns to step 214 where another combination of molecular markers is selected and, at step 216, this new combination of molecular markers is evaluated using a mathematical model applied to the molecular marker data of the new combination. In some embodiments, the candidate molecular marker list comprises less than 25, less than 24, less than 23, less than 22, less than 21, or less than 20 molecular markers at step 214. In some embodiments, step 218 requires that a classifier be computed for all possible combinations of molecular markers. In other embodiments, step 218

requires that classifiers for only a portion of the possible combinations of molecular markers be considered.

In some embodiments, some aspects of steps 214-218 are performed by molecular marker classifier evaluation module 62. In fact, in some embodiments, several  
5 different software programs, such as Microsoft (Redmond, Washington) Excel, are used in steps 214-218.

*Step 220.*

Once all the desired classifiers have been computed by loop 214-218, the classifiers are evaluated to determine which of the classifiers are most effective. In one embodiment  
10 the resulting classifiers of loop 214-218 are scored. In some embodiments, scoring is done using the training population 44. In other embodiments, scoring is done using a "scoring population" wherein the scoring population includes at least some members not present in the training population. In one embodiment, the scoring population includes members of the training population in addition to one or more members not used in the training  
15 population. In some embodiments, five percent or less, ten percent or less, twenty percent or less, thirty percent or less, fifty percent or less, or ninety percent or less of the members of the training population are common to the scoring population.

In some embodiments, the Percent Correct Predictions statistic is used to score each classifier. The "Percent Correct Predictions" statistic assumes that if the estimated p  
20 is greater than or equal to 0.5, then the event is expected to occur and to not occur otherwise. By assigning these probabilities zeros and ones, a comparison can be made to the values of the samples in the training population to determine what percentage of the training population was sampled correctly.

In some embodiments, ROC analysis is performed and is used to score the  
25 classifiers. In one embodiment, the area under the ROC curve is used to judge the quality of the classifier. As would be understood by those of skill in the relevant arts, area under the curve converts the two dimensional information contained in the ROC curve into one dimensional information. In other embodiments, information from the two dimensional aspect of the ROC curve is utilized directly. For example, the ROC curve also provides  
30 information with respect to the sensitivity and specificity of the classifier. In some embodiments, classifiers are selected on the basis of either sensitivity or specificity. This can be an important scoring indicator. For example, a diagnostic classifier with high sensitivity (ie high true positive rate and low false negative rate may be important in situations where it is safer to misdiagnosis an individual as having disease rather than

misdiagnosing a disease bearing person as normal. Therefore in some embodiments, a cutoff can be set for either sensitivity or specificity and the classifier ranked or scored on the basis of the remaining variable. In some embodiments, ROC curves are generated for each model computed in an instance of step 216 using data obtained in step 206 for members of either the training population or scoring population or both.

In some embodiments, the classifier resulting from the application of the mathematical itself results in a score as to the accuracy of the model. In this embodiment, the score is based on the accuracy of the model within the training population only.

In some embodiments, a classifier is a weighted logistic regression model characterized by a multicategory logit model. For example, in some embodiments, a classifier discriminates between two different trait groups. In other embodiments, a classifier discriminates between more than two different trait groups. Logit models, including multicategory logit models are described in Agresti, *An Introduction to Categorical Data Analysis*, John Wiley & Sons, Inc., 1996, New York, Chapters 7 and 8, which is hereby incorporated by reference. Table E illustrates the data that is used to form an ROC curve based on expression data applied to a mathematical model that uses the logit:

$$\ln[p/(1-p)] = \alpha + \beta_1 X_1 + \beta_2 X_2 + \varepsilon$$

Table E: Values for the logit  $\ln[p/(1-p)] = \alpha + \beta_1 X_1 + \beta_2 X_2 + \varepsilon$  using hypothetical values for training population 44

$\ln[p/(1-p)]$	Presence / Absence of a Trait
0.98	Y
0.97	Y
0.95	Y
0.93	Y
0.91	N
0.11	Y
0.07	N
0.03	N

Each row in Table E corresponds to a different specimen in the scoring population. The left column represents the results of the logit for the classifier being sampled. The specimens in Table E are ranked by the logit score listed in the left hand column. The

right hand column details the presence or absence of the trait that is being considered by the regression equation. Table E can be used to compute a ROC curve using the same techniques disclosed in step 208 (in which each row in Table E is considered a threshold cutoff value in order to compute ROC curve datapoints). Then, the area under the ROC curve can be computed in order to assess the predictive quality of the classifier.

In step 220, each classifier is scored using any of the techniques disclosed here or that are known in the art. The classifiers can then be ranked based on their score. For example, they can be ranked based on the percent correct predictions, area under the ROC curve, sensitivity or specificity or some weighted or unweighted combination of the two scoring techniques. In some embodiments, step 220 is performed by molecular marker evaluation module 64.

*Step 222.*

Step 222 is optional. Optional step 222 provides additional filtering to eliminate some of the candidate classifiers computed in loop 214-218. In one such filter, limited to the case in which the classifiers computed in steps 214-218 are based on application of data to regression based mathematical models, classifiers that have at least one coefficient that is large are eliminated. Such classifiers have the potential to magnify small errors in the data. In some embodiments, determination as to whether or not a coefficient is large can require multiple computation steps. In instances where a coefficient uniquely represents a molecular marker, the maximum value (MAX) for the data measured for the molecular marker in a trait subgroup associated with the classifier is identified. For example, consider the case in which a given coefficient uniquely represents the expression of gene A in blood. Further suppose that low throughput data for gene A from 10 individuals of a particular trait subgroup was measured in step 206. The value MAX would be the largest expression value observed for gene A in the ten individuals from the subject trait subgroup. For example, if individual #7 in the set of ten individuals exhibited the highest expression level for gene A as determined by the methods of step 206, then the expression value measured for gene A in individual #7 will represent MAX. Next, the minimum value (MIN) for the data measured for the molecular marker in the subject trait subgroup is identified. In the example presented above, MIN is the expression level of gene A in the subject having the lowest expression level for gene A in the set of ten subjects as determined by the low throughput measurement methods of step 206. Next, the coefficient derived in the regression for the unique molecular marker (*e.g.*, the coefficient for gene A) is multiplied by the difference between (MAX) and (MIN) in order to obtain

the test value (TEST). In other words, for each coefficient  $i$  in a classifier, the following equation is computed:

$$\text{TEST}_i = \text{coefficient}_i * [\text{MAX} - \text{MIN}].$$

As an example, consider the case in which a classifier is used to determine whether or not a subject has a particular cancer. In this case, one of the trait subgroups in training population 44 will represent patients that have this cancer. To evaluate a coefficient of a classifier in this case, the low value and high value for the measured data of the molecular marker  $i$  in the trait subgroup is obtained and the difference between these two values is multiplied against the coefficient value in order to obtain the value of  $\text{TEST}_i$ . In some embodiments, a coefficient  $i$  is considered large and the classifier that includes the coefficient is discarded when the value is greater than 5, greater than 10, greater than 100 or greater than 1000.

In typical embodiments, a classifier will determine whether a subject falls into one of at least two different trait subgroups. In other words, the classifier will discriminate between at least two different trait subgroups. A test has been presented above for determining whether a coefficient in a regression derived classifier is too large. This test used one of the trait subgroups that the classifier discriminates. In some embodiments, the test is repeated for each of the trait subgroups that the classifier can discriminate. For example, in the case of a classifier that can discriminate between the cancerous trait subgroup and the non-cancerous trait subgroup, the test is independently run using data from each trait subgroup. That is, the test is first run using only data from the cancerous trait subgroup and then the test is run a second time using only data from the non-cancerous trait subgroup. If a coefficient is too large in any such independent test, the classifier is eliminated from further consideration. In some embodiments, the test is run against only one of the possible trait subgroups that the subject classifier can discriminate.

In another embodiment, some classifiers are eliminated on the basis of the score. For example, where the scoring system used is receiver operating characteristic (ROC) curve score determined by an area under the ROC curve, in some embodiments, those classifiers with scores of less than 0.95, 0.9, 0.85, 0.8, 0.7, 0.65, 0.6, 0.55, 0.5 or 0.45 or less can be eliminated. In other embodiments, where specificity is important to the use of the classifier, a sensitivity threshold can be set and classifiers ranked on the basis of the specificity. For example with a cutoff for specificity of less than 0.95, 0.9, 0.85, 0.8, 0.7, 0.65, 0.6, 0.55, 0.5 or 0.45 or less can be eliminated. Similarly, the specificity threshold can be set and classifiers ranked on the basis of sensitivity for example with a cutoff for



sensitivity of less than 0.95, 0.9, 0.85, 0.8, 0.7, 0.65, 0.6, 0.55 0.5 or 0.45 or less can be eliminated. Thus in some embodiments, only the top 10 ranking classifiers, the top 20 ranking classifiers, or the top 100 ranking classifiers are selected and the remaining classifiers eliminated.

5           *Step 224.*

After classifiers have been scored and ranked and some classifiers optionally eliminated; one or more classifiers can be combined to create a classifier group. For instance, in some embodiments, the top 10 ranking classifiers, the top 20 ranking classifiers, or the top 100 ranking classifiers are selected. In some embodiments, any of  
10 the top 1 to top 500 ranking classifiers is selected. In instances where more than one classifier is selected, in one embodiment, each classifier contributes one vote to the diagnosis of the test subject such that diagnosis of the test subject is determined as a result of a combination of classifiers. In other embodiments, multiple classifiers can be used and different weighting schema applied to each classifier. For example, weighting schema can  
15 include weighting on the basis of factors such as the original score the classifier, the logs odd ratio ("logit"), the size of the coefficients for each classifier, some combination thereof and the like.

*Step 226.*

Step 226 is optional. Optional step 226 is useful if training population 44 is  
20 comprised of more than two trait subgroups. In cases where there are more than two trait subgroups, multiple binary classifiers (or groups of said classifiers) can be developed wherein each binary classifier (or group of said classifiers) is directed towards differentiating as between two traits. In one embodiment, each round of the funnel (e.g. steps 202, 204, 206, 214, 216, 220 and 224) produces a set of binary classifiers. In another  
25 embodiment, multiple lists of binary candidate molecular markers are developed by performing step 202, and then binary classifiers (or groups of binary classifiers) are developed by proceeding with multiple rounds of the remainder of the funnel (e.g. steps 204, 206, 214, 216, 220 and step 224). Because each classifier represents only a binary test e.g. the absence or presence of a single trait, in step 226 a determination is made as to  
30 whether all classifiers have been developed for training population 44. If not (226-No), process control returns to step 210 and work is initiated to develop a classifier for a different trait represented by training population 44. Therefore, steps 210-224 can optionally be repeated until one or more classifiers or groups of classifiers have been selected for each of the trait subgroups represented by training population 44.

In some embodiments, each classifier or group of classifiers developed in accordance with embodiments of the present invention is stored in classifier database 70. Fig. 5 illustrates an exemplary classifier database 70 in accordance with one embodiment of the present invention. Database 70 includes an entry 400 for each classifier 400. Each classifier 400 is optionally given a classifier name 402. Each classifier 400 is part of classifier. For example, a given classifier can consist of only a single classifier. In other embodiments, a given classifier can consist of one or a plurality of classifiers. Therefore, each classifier 402 includes an indicator 403 to indicate which classifier the classifier is in. Further, each classifier 400 has an optional indicator 404 to indicate the trait that the classifier can discriminate. In some embodiments, optional indicator indicates the trait subgroups that the classifier can discriminate. In some embodiments such information can be inferred from the classifier identifier field 403 since each classifier represents the absence or presence of a particular trait (e.g., absence or presence of cancer). In addition to this header information, each classifier includes the identity 406 of one or more molecular markers and the respective coefficients 408 for each of the molecular markers.

Once classifiers or classifier groups have been developed, the classifiers can be used to diagnose a patient that has presented as possibly having a disease that can be differentiated by the classifiers. Figure 3 is a flowchart of a method of applying the classifiers to a patient.

*Step 328.*

Step 328 can be performed after the previously described steps, or can be used in conjunction with a classifier or classifier groups derived using the methods disclosed herein. As such, steps 328-334 represent a completely independent method of the present invention and can be performed at any time once suitable classifiers have been developed using, for example, steps 301 through 326. Step 328 is used in conjunction with step 330 to diagnose a trait of interest of an individual not represented in either the training population or the scoring population (a "test individual"). Each classifier or classifier group identified previously can be used to determine whether a test individual has a trait of interest. In order to perform such tests, molecular marker data for each molecular marker of the classifier or classifier group of interest is required. To obtain such data, a sample of blood from the subject is obtained using any of the techniques described in Section 5.2. The sample is used to measure molecular marker data for each molecular marker in the sample using any of the techniques described in Sections 5.3 or 5.4. Thus in step 328, once classifiers have been identified, molecular marker data for use with the classifier or

classifier groups can be obtained using either high throughput or low throughput techniques.

Advantageously, the molecular marker data obtained in step 328 can be stored in patient database 68 for later use. In fact, in some embodiments, rather than obtaining molecular marker data from a patient sample in step 328, the data is obtained from a subject in patient database 68. In such embodiments, the molecular marker data was previously loaded into patient database 68.

Fig. 6 illustrates a patient database 68 in accordance with one embodiment of the present invention. There is a record 500 for each patient (subject) tracked by patient database 68. Each patient record 500 optionally includes a patient identifier 502 to uniquely identify the patient. In some embodiments such unique identifiers can be inferred from the patient record value 500. Each patient record 500 includes a molecular profile 504 comprising molecular marker data collected for a plurality of molecular marker products from a sample defined in Section 5.2 using any one of the techniques described in Sections 5.3 and 5.4. In typical embodiments, a molecular profile 504 includes a plurality of molecular marker identities 506 and the corresponding measured molecular marker data values 508 for such molecular markers. In addition to the molecular profile, each patient record 502 can include one or more traits 510. Such trait characterizations can be assigned by observation of the subject and/or by testing the patient's molecular profile using the classifiers constructed in accordance with the methods of the present invention. Section 5.10, below, provides more details on exemplary patient databases 68.

#### *Step 330.*

In step 330 the classifier created using some or more of the previous steps is used to diagnose a test individual. In some embodiments diagnosis can be performed using a classifier group from step 224. For example, in one embodiment, where there are numerous classifiers after step 222 that provide satisfactory scores (given the purpose for use), a test subject can be diagnosed by using the results of all or some of these classifiers in the form of a classifier group as described in step 224. In one embodiment, the term diagnosis means the results of a single classifier or group of classifiers resulting from the application of the funneling method described in steps 202-224. For example, the resulting classifier or group of classifiers will enable the ability to determine whether a test individual belongs to one of two possible trait subgroups. In another embodiment, by the term diagnosis is meant the results of multiple classifiers or multiple groups of classifiers (ie classifiers resulting from the application of more than one round of the funneling

method described in steps 202 – 224). For example, the resulting classifiers or groups of classifiers used in series can allow a diagnosis as to whether an individual belongs to one of three or more possible trait subgroups (e.g. results of first classifier distinguish as to whether person has schizophrenia or does not have schizophrenia – If not schizophrenia  
5 apply a second classifier or group of classifiers to determine whether individual has bipolar disorder or does not have bipolar disorder etc.) The use of the classifiers to diagnose depends upon the trait subgroups used to develop the classifier. For example, if the classifier was developed to differentiate as between two trait subgroups, the classifier can be used to diagnose a test subject as being either of the first trait subgroup or the second  
10 trait subgroup. To diagnose a test subject, preferably a quantitative technique such as quantitative RT-PCR is utilized to obtain molecular marker data measured in step 328 is used.

To illustrate the use of a classifier to diagnose, consider the case in which the classifier comprises the classifier group:

$$15 \quad \ln[p/(1-p)] = 0.34 + 0.24X_1 + 0.74X_3 + 0.03,$$

$$\ln[p/(1-p)] = 0.54 - 0.4X_2 + 0.83X_3 + 0.01.$$

That is, the exemplary classifier group consisting of two classifiers. To poll the classifier, the data (*e.g.* abundance level, activity level, *etc.*) for molecular markers  $X_1$ ,  $X_2$  and  $X_3$  is measured using any of the techniques described in Section 5.3 or 5.4. Then,  
20 these data measurement values are placed into the classifier equations and the equations are processed and the output is used to predict outcome. In one embodiment, classifier equation values that approach a value of one indicate that the sample has the trait associated with the classifier whereas classifier equation values that approach zero indicate that the sample does not have the trait associated with the classifier. In other  
25 embodiments, the equations are regressed so that the opposite relationship hold (*e.g.*, equation values approach one indicate absence of an associated trait). In one embodiment, each equation is assigned a “+1” vote if the equation approaches one or a “-1” vote if the equation approaches zero. Equation votes are summed. If the net summation is positive, then the subject is deemed to have the trait associated with the classifier. If the net  
30 summation is negative, then the subject is deemed not to have the trait associated with the classifier. In some embodiments, step 330 is performed by model polling and reporting module 66.

*Step 332.*

One of the advantages of the present invention is that a single sample collected in accordance with Section 5.2 can be used to test the patient for one or more of a plurality of molecular markers which may be useful for one or more traits. Accordingly, in step 332, a determination is made as to whether the patient has been tested for each pair of traits for which a determination is required. If additional determinations are required (332-No), process control is returned to step 330 and the measured molecular marker data from the patient is used to help determine the likelihood as to whether a subject has other traits represented by a trait subgroup in training population 44.

*Step 334.*

When the patient sample has been used to determine if the subject has any of a plurality of different traits as determined by one or more classifiers or classifier groups, a report is generated. In some embodiments, this report includes the results of each classification test. In other words, the report provides an indication as to whether it is likely the tested subject has any one of a plurality of different traits. In some embodiments, step 334 is performed by classifier polling and reporting module 66. Section 5.5 provides a summary of some of the applications for classifiers constructed using the methods of the present invention.

## **5.2 SOURCE OF MOLECULAR MARKER DATA**

The present invention provides methods for identifying molecular markers by obtaining molecular marker data which represents the products of molecular markers found in a blood sample. Molecular markers are thus identified that correlate with, are associated with, or indicate a trait. The present invention also provides methods for detecting, diagnosing, monitoring, prognosing or predicting a trait or reoccurrence of a trait based upon data corresponding to the expression of molecular markers in a blood sample. As used herein, the terms "subject" and "patient" and "individual" are used interchangeably to refer to an animal (e.g., a mammal, a fish, an amphibian, a reptile, a bird, and an insect). In a specific embodiment, a subject is a mammal (e.g., a non-human mammal and a human). In another embodiment, a subject is a pet (e.g., a dog, a cat, a guinea pig, a monkey and a bird), a farm animal (e.g., a horse, a cow, a pig, a goat and a chicken) or a laboratory animal (e.g., a mouse and rat). In another embodiment, the subject is a primate (e.g., a chimpanzee and a human). In a preferred embodiment, the subject is a human.

### 5.2.1 SOURCE OF A BLOOD SAMPLE

A blood sample obtained from any subject may be used in accordance with the methods of the invention. Examples of subjects from which a blood sample can be obtained and utilized in accordance with the methods of the invention include, but are not limited to, asymptomatic subjects, subjects manifesting or exhibiting 1, 2, 3, 4 or more traits or symptoms of a trait, subjects clinically diagnosed as having a trait, subjects predisposed to a trait (*e.g.*, subjects with a family history of a trait, subjects with a genetic predisposition to a trait, and subjects that lead a lifestyle that predisposes them to a trait or increases the likelihood of contracting a trait), subjects suspected of having a trait, subjects undergoing therapy for a trait, subjects non-responsive to a therapy, subjects responsive to a therapy, subjects with more than one trait (*e.g.*, subjects with 2, 3, 4, 5 or more traits), subjects not undergoing therapy for a trait, subjects determined by a medical practitioner (*e.g.*, a physician) to be healthy or disease-free, subjects that are in remission, subjects cured of trait, and subjects that have not been diagnosed with a condition. In specific embodiment, the condition is a disease. In another specific embodiment, a condition is any state that is codified in the *International Classification of Diseases*, 9<sup>th</sup> Revision, Department of Health and Human Services (ICD-9 codes) and/or SNOMED Clinical Terms (SNOMED CT®) which is hereby incorporated by reference, or equivalent treatise.

Non-limiting examples of disease include, but are not limited to, blood disorder, blood lipid disease, autoimmune disease, arthritis (*e.g.*, osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis and the like), bone or joint disorder, lupus, an allergy, a cardiovascular disorder (*e.g.*, heart failure, congenital heart disease, rheumatic fever, valvular heart disease, cor pulmonale, cardiomyopathy, myocarditis, pericardial disease, vascular diseases such as atherosclerosis, acute myocardial infarction, ischemic heart disease and the like), obesity, respiratory disease (*e.g.*, asthma, pneumonitis, pneumonia, pulmonary infections, lung disease, bronchiectasis, tuberculosis, cystic fibrosis, interstitial lung disease, chronic bronchitis emphysema, pulmonary hypertension, pulmonary thromboembolism, acute respiratory distress syndrome and the like), hyperlipidemias, endocrine disorder, immune disorder, infectious disease, muscle wasting and whole body wasting disorder, neurological disorder (*e.g.*, migraines, seizures, epilepsy, cerebrovascular disease, Parkinson's, ataxic disorders, motor neuron diseases, cranial nerve disorders, spinal cord disorders, meningitis and the like), neurodegenerative disease (*e.g.*, alzheimers, dementia and the like), neuropsychiatric disease (*e.g.*, schizophrenia, anxiety and the like), mood disorders (*e.g.*, bipolar disorder; manic depression and the like), skin disorder,

kidney disease, scleroderma, stroke, hereditary hemorrhage telangiectasia, diabetes, disorders associated with diabetes (e.g., PVD), hypertension, Gaucher's disease, cystic fibrosis, sickle cell anemia, liver disease, stomach disease, pancreatic disease, eye disease, ear disease, nose disease, throat disease, diseases affecting the reproductive organs, gastrointestinal diseases (including diseases of the colon, diseases of the spleen, appendix, gall bladder, and others) and the like. For further discussion of human diseases, see Mendelian Inheritance in Man: A Catalog of Human Genes and Genetic Disorders by Victor A. McKusick (12th Edition, 3 volume set, June 1998, Johns Hopkins University Press, ISBN: 0801857422) and Harrison's Principles of Internal Medicine by Braunwald, Fauci, Kasper, Hauser, Longo, & Jameson (15th Edition 2001), the entirety of each of which is incorporated herein. Additional examples of disease are disclosed in Section 5.8, below.

In one embodiment of the invention, the disease is an immune disorder, such as those associated with overexpression of a gene or expression of a mutant gene (e.g., autoimmune diseases, such as diabetes mellitus, arthritis (including rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, and psoriatic arthritis), multiple sclerosis, encephalomyelitis, myasthenia gravis, systemic lupus erythematosus, automimmune thyroiditis, dermatitis (including atopic dermatitis and eczematous dermatitis), psoriasis, Sjogren's Syndrome, Crohn's disease, aphthous ulcer, iritis, conjunctivitis, keratoconjunctivitis, ulcerative colitis, asthma, allergic asthma, cutaneous lupus erythematosus, scleroderma, vaginitis, proctitis, drug eruptions, leprosy reversal reactions, erythema nodosum leprosum, autoimmune uveitis, allergic encephalomyelitis, acute necrotizing hemorrhagic encephalopathy, idiopathic bilateral progressive sensorineural hearing, loss, aplastic anemia, pure red cell anemia, idiopathic thrombocytopenia, polychondritis, Wegener's granulomatosis, chronic active hepatitis, Stevens-Johnson syndrome, idiopathic sprue, lichen planus, Graves' disease, sarcoidosis, primary biliary cirrhosis, uveitis posterior, and interstitial lung fibrosis), graft-versus-host disease, cases of transplantation, and allergy.

In another embodiment, a disease of the invention is a cellular proliferative and/or differentiative disorder that includes, but is not limited to, cancer, e.g., carcinoma, sarcoma or other metastatic disorders and the like. As used herein, the term "cancer" refers to cells having the capacity for autonomous growth, i.e., an abnormal state of condition characterized by rapidly proliferating cell growth. "Cancer" is meant to include all types of cancerous growths, pre-cancerous growths or lesions, oncogenic processes, metastatic

tissues or malignantly transformed cells, tissues, or organs, irrespective of histopathologic type or stage of invasiveness. Examples of cancers include, but are not limited to, solid tumors, tissue specific tumors, benign cancer, metastatic cancers, early stage cancer, late stage cancer and leukemias, including: apudoma, choristoma, branchioma, malignant

5 carcinoid syndrome, carcinoid heart disease, carcinoma (e.g., Walker, basal cell, basosquamous, Brown-Pearce, ductal, Ehrlich tumour, in situ, Krebs 2, Merkel cell, mucinous, non-small cell lung, oat cell, papillary, scirrhus, bronchiolar, bronchogenic, squamous cell, and transitional cell), histiocytic disorders, leukaemia (e.g., B cell, mixed

10 cell, null cell, T cell, T-cell chronic, HTLV-II-associated, lymphocytic acute, lymphocytic chronic, mast cell, and myeloid), histiocytosis malignant, Hodgkin disease, immunoproliferative small, non-Hodgkin lymphoma, plasmacytoma, reticuloendotheliosis, melanoma, chondroblastoma, chondroma, chondrosarcoma, fibroma, fibrosarcoma, giant cell tumors, histiocytoma, lipoma, liposarcoma, mesothelioma, myxoma, myxosarcoma, osteoma, osteosarcoma, Ewing sarcoma, synovioma, adenofibroma, adenolymphoma,

15 carcinosarcoma, chordoma, craniopharyngioma, dysgerminoma, hamartoma, mesenchymoma, mesonephroma, myosarcoma, ameloblastoma, cementoma, odontoma, teratoma, thymoma, trophoblastic tumour, adeno-carcinoma, adenoma, cholangioma, cholesteatoma, cylindroma, cystadenocarcinoma, cystadenoma, granulosa cell tumour, gynandroblastoma, hepatoma, hidradenoma, islet cell tumour, Leydig cell tumour,

20 papilloma, Sertoli cell tumour, theca cell tumour, leiomyoma, leiomyosarcoma, myoblastoma, myoma, myosarcoma, rhabdomyoma, rhabdomyosarcoma, ependymoma, ganglioneuroma, glioma, medulloblastoma, meningioma, neurilemmoma, neuroblastoma, neuroepithelioma, neurofibroma, neuroma, paraganglioma, paraganglioma nonchromaffin, angiokeratoma, angiolymphoid hyperplasia with eosinophilia, angioma sclerosing,

25 angiomatosis, glomangioma, hemangioendothelioma, hemangioma, hemangiopericytoma, hemangiosarcoma, lymphangioma, lymphangiomyoma, lymphangiosarcoma, pinealoma, carcinosarcoma, chondrosarcoma, cystosarcoma, phyllodes, fibrosarcoma, hemangiosarcoma, leiomyosarcoma, leukosarcoma, liposarcoma, lymphangiosarcoma, myosarcoma, myxosarcoma, ovarian carcinoma, rhabdomyosarcoma, sarcoma (e.g.,

30 Ewing, experimental, Kaposi, and mast cell), neoplasms (e.g., bone, breast, digestive system, colorectal, liver, pancreatic, pituitary, testicular, orbital, head and neck, central nervous system, acoustic, pelvic respiratory tract, and urogenital), neurofibromatosis, and cervical dysplasia, and other conditions in which cells have become immortalized or transformed.



### 5.2.2 METHODS FOR COLLECTING BLOOD

In one aspect, a sample of blood is obtained from a subject according to methods well known in the art. The present invention can use whole blood, but can also use blood in which the serum or plasma has been removed and the RNA or mRNA isolated from the remaining sample in accordance with methods known in the art (for example, using  
5 preferably gentle centrifugation at 300-800xg for five to ten minutes).

In some embodiments a drop of blood is collected from a simple pin prick made in the skin of a subject. In such embodiments, this drop of blood collected from a pin prick is all that is needed. A drop of blood can include volumes of anywhere from 10ul through to  
10 100ul. Blood may be drawn from a subject from any part of the body (*e.g.*, a finger, a hand, a wrist, an arm, a leg, a foot, an ankle, a stomach, and a neck) using techniques known to one of skill in the art, in particular methods of phlebotomy known in the art. In a specific embodiment, venous blood is obtained from a subject and utilized in accordance with the methods of the invention. In another embodiment, arterial blood is obtained and  
15 utilized in accordance with the methods of the invention. The composition of venous blood varies according to the metabolic needs of the area of the body it is servicing. In contrast, the composition of arterial blood is consistent throughout the body. For routine blood tests, venous blood is generally used.

Venous blood can be obtained from any source including the basilic vein, cephalic  
20 vein, or median vein. Arterial blood can be obtained from the radial artery, brachial artery or femoral artery. A vacuum tube, a syringe or a butterfly may be used to draw the blood. Typically, the puncture site is cleaned, a tourniquet is applied approximately 3-4 inches above the puncture site, a needle is inserted at about a 15-45 degree angle, and if using a vacuum tube, the tube is pushed into the needle holder as soon as the needle penetrates the  
25 wall of the vein. When finished collecting the blood, the needle is removed and pressure is maintained on the puncture site. Usually, heparin or another type of anticoagulant is in the tube or vial that the blood is collected in so that the blood does not clot. When collecting arterial blood, anesthetics can be administered prior to collection.

The amount of blood collected will vary depending upon the site of collection, the  
30 amount required for a method of the invention, and the comfort of the subject. However, an advantage of one embodiment of the present invention is that the amount of blood required to implement the methods of the present invention can be so small that more invasive procedures are not required to obtain the sample. For example, in some embodiments, all that is required is a drop of blood. This drop of blood can be obtained,

for example, from a simple pinprick. In some embodiments, any amount of blood is collected that is sufficient to measure molecular marker data. As such, in some embodiments, the amount of blood that is collected is 1  $\mu$ l or less, 0.5  $\mu$ l or less, 0.1  $\mu$ l or less, or 0.01  $\mu$ l or less. However, the present invention is not limited to such  
5   embodiments. In some embodiments more blood is available and in some embodiments, more blood can be used to effect the methods of the present invention. As such, a broad range of blood volumes is contemplated and can be used to obtain the molecular marker data measurement data used in the present invention. In various specific embodiments, 0.001 ml, 0.005 ml, 0.01 ml, 0.05 ml, 0.1 ml, 0.15 ml, 0.2 ml, 0.25 ml, 0.5 ml, 0.75 ml, 1  
10   ml, 1.5 ml, 2 ml, 3 ml, 4 ml, 5 ml, 10 ml, 15 ml or more of blood is collected from a subject. In other specific embodiments, 0.001 ml to 15ml, 0.01 ml to 10 ml, 0.1 ml to 10 ml, 0.1 ml to 5 ml, 1 to 5 ml of blood is collected from a subject.

In some embodiments of the present invention, blood is stored within a K3/EDTA tube. In another embodiment, one can utilize tubes for storing blood which contain  
15   stabilizing agents such as disclosed in United States patent No. 6,617,170. In another embodiment, the PAXgene™ blood RNA system provided by PreAnalytiX, a Qiagen/BD company, can be used to collect blood. In yet another embodiment, the Tempus™ blood RNA collection tubes, offered by Applied Biosystems, can be used. Tempus™ collection tubes provide a closed evacuated plastic tube containing RNA stabilizing reagent for  
20   whole blood collection.

The collected blood is optionally but preferably stored at refrigerated temperatures, such as 4 °C, prior to molecular marker data measurement. In some embodiments, a portion of the blood sample is used for molecular measurement at a first instance of time whereas one or more remaining portions of the blood sample is stored for a period of time  
25   for later use. This period of time can be an hour or more, a day or more, a week or more, a month or more, a year or more, or indefinitely. For long term storage, storage methods well known in the art, such as storage at cryo temperatures (*e.g.* below -60 °C) can be used. In some embodiments, in addition to storage of the blood (or instead of storage of the blood), isolated molecular markers (*e.g.*, nucleic acid, protein, carbohydrates, lipids,  
30   metabolites, *etc.*) are stored for a period of time for later use. Storage of such molecular markers can be for an hour or more, a day or more, a week or more, a month or more, a year or more, or indefinitely.

### 5.2.3 METHOD OF ISOLATING BLOOD CELLS

In some embodiments of the present invention, whole blood is used directly to isolate and analyze the products of one or more molecular markers so as to obtain molecular marker data. In other embodiments of the invention fractionated blood can be used. By fractionated blood is meant blood in which the blood cells are separated prior to isolation of the molecular markers using techniques known in the art. For example, fractionated blood includes blood wherein the blood cells are fractionated using Ficoll-Hypaque (Pharmacia) gradient centrifugation. Such centrifugation separates erythrocytes (red blood cells) from various types of nucleated cells and from plasma. As such, in some embodiments of the present invention, a blood sample of the invention is fractionated blood. In one embodiment, peripheral blood leukocytes are utilized ("PBLs"). PBLs are separated from the remainder of the blood using a Ficoll® gradient.

By way of example but not limitation, macrophages can be obtained as follows. Mononuclear cells are isolated from peripheral blood of a subject, by syringe removal of blood followed by Ficoll-Hypaque gradient centrifugation. Tissue culture dishes are pre-coated with the subject's own serum or with AB+ human serum and incubated at 37°C for one hour. Non-adherent cells are removed by pipetting. Cold (4°C) 1mM EDTA in phosphate-buffered saline is added to the adherent cells left in the dish and the dishes are left at room temperature for fifteen minutes. The cells are harvested, washed with RPMI buffer and suspended in RPMI buffer. Increased numbers of macrophages can be obtained by incubating at 37°C with macrophage-colony stimulating factor (M-CSF). Antibodies against macrophage specific surface markers, such as Mac-1, can be labeled by conjugation of an affinity compound to such molecules to facilitate detection and separation of macrophages. Affinity compounds that can be used include but are not limited to biotin, photobiotin, fluorescein isothiocyanate (FITC), or phycoerythrin (PE), or other compounds known in the art. Cells retaining labeled antibodies are then separated from cells that do not bind such antibodies by techniques known in the art such as, but not limited to, various cell sorting methods, affinity chromatography, and panning.

Blood cells can be fractionated using a fluorescence activated cell sorter (FACS). Fluorescence activated cell sorting (FACS) is a known method for separating particles, including cells, based on the fluorescent properties of the particles. See, for example, Kamarch, 1987, Methods Enzymol 151:150 165. Laser excitation of fluorescent moieties in the individual particles results in a small electrical charge allowing electromagnetic separation of positive and negative particles from a mixture. An antibody

or ligand used to detect a blood cell antigenic determinant present on the cell surface of particular blood cells is labeled with a fluorochrome, such as FITC or phycoerythrin. The cells are incubated with the fluorescently labeled antibody or ligand for a time period sufficient to allow the labeled antibody or ligand to bind to cells. The cells are processed through the cell sorter, allowing separation of the cells of interest from other cells. FACS sorted particles can be directly deposited into individual wells of microtiter plates to facilitate separation.

Magnetic beads can be also used to separate blood cells in some embodiments of the present invention. For example, blood cells can be sorted using a magnetic activated cell sorting (MACS) technique, a method for separating particles based on their ability to bind magnetic beads (0.5 100  $\mu$ m diameter). A variety of useful modifications can be performed on the magnetic microspheres, including covalent addition of an antibody which specifically recognizes a cell solid phase surface molecule or hapten. A magnetic field is then applied, to physically manipulate the selected beads. In a specific embodiment, antibodies to a blood cell surface marker are coupled to magnetic beads. The beads are then mixed with the blood cell culture to allow binding. Cells are then passed through a magnetic field to separate out cells having the blood cell surface markers of interest. These cells can then be isolated.

In some embodiments, the surface of a culture dish may be coated with antibodies, and used to separate blood cells by a method called panning. Separate dishes can be coated with antibody specific to particular blood cells. Cells can be added first to a dish coated with blood cell specific antibodies of interest. After thorough rinsing, the cells left bound to the dish will be cells that express the blood cell markers of interest. Examples of cell surface antigenic determinants or markers include, but are not limited to, CD2 for T lymphocytes and natural killer cells, CD3 for T lymphocytes, CD11a for leukocytes, CD28 for T lymphocytes, CD19 for B lymphocytes, CD20 for B lymphocytes, CD21 for B lymphocytes, CD22 for B lymphocytes, CD23 for B lymphocytes, CD29 for leukocytes, CD14 for monocytes, CD41 for platelets, CD61 for platelets, CD66 for granulocytes, CD67 for granulocytes and CD68 for monocytes and macrophages.

Whole blood can also be fractionated into cells types such as leukocytes, platelets, erythrocytes, etc. Leukocytes can be further separated into granulocytes and agranulocytes using standard techniques. Granulocytes can be separated into cell types such as neutrophils, eosinophils, and basophils using standard techniques. Agranulocytes can be separated into lymphocytes (e.g., T lymphocytes and B lymphocytes) and monocytes using

standard techniques. T lymphocytes can be separated from B lymphocytes and helper T cells separated from cytotoxic T cells using standard techniques. Separated blood cells (e.g., leukocytes) can be frozen by standard techniques prior to use in the present methods.

#### **5.2.4 BLOOD SAMPLES USED IN METHODS OF THE INVENTION**

5           In accordance with the methods of the invention, the term "blood sample" can include any of the samples discussed in section 5.2.3. In some embodiments, this includes whole blood, fractionated blood, a sample of subsets of fractionated blood, and a sample of specific types of blood cells. In a specific embodiment, the whole blood sample can have the plasma or serum removed by centrifugation, using preferably gentle  
10       centrifugation at 300-800xg for five to ten minutes.

          In another embodiment, a blood sample of the invention is a sample of peripheral blood leukocytes (PBLs). In another embodiment, a blood sample of the invention is a sample of granulocytes. In another embodiment, a blood sample of the invention is a sample of neutrophils, eosinophils, basophils or any combination thereof. In another  
15       embodiment, a blood sample of the invention is a sample of agranulocytes. In another embodiment, a blood sample of the invention is a sample of lymphocytes, monocytes or a combination thereof. In yet another embodiment, a blood sample of the invention is a sample of T lymphocytes, B lymphocytes or a combination thereof. See, e.g., Section 5.4.3 supra for methods of isolating blood cells.

20           A blood sample that is useful according to the invention is in an amount that is sufficient for the detection of one or more molecular markers according to the invention. In a specific embodiment, a blood sample useful according to the invention is in an amount ranging from 1  $\mu$ l to 100 ml, preferably 10  $\mu$ l to 50 ml, more preferably 10  $\mu$ l to 25 ml and most preferably 10  $\mu$ l to 1 ml.

25           In one embodiment whole blood, or serum free whole blood is taken and the red blood cells are lysed with lysing buffer. In a specific embodiment, the Lysis Buffer (1L) consists of 0.6g EDTA 1.0g KHCO<sub>2</sub>, and 8.2g NH<sub>4</sub>Cl adjusted to pH 7.4 (using NaOH). Once mixed with lysing buffer, the sample is centrifuged and the cell pellet retained and RNA or mRNA extracted in accordance with methods known in the art  
30       ("lysed whole blood") (see, for example, Sambrook, Fritsch & Maniatis, "Molecular Cloning: A Laboratory Manual (1982); "DNA Cloning: A Practical Approach," Volumes I and II (D.N. Glover ed. 1985). The use of whole blood or lysed whole blood is preferred since it avoids the costly and time-consuming need to separate out the cell types within the blood (Liew et al. U.S. Patent Application No.US 2004/0014059). In another

embodiment, whole blood is stored and stabilized using PAXgene® tubes and RNA can be isolated using the PAXgene® RNA Isolation system. In yet another embodiment, RNA is isolated from whole blood which has been isolated using PAXgene® and additional globin reduction protocols followed.

### 5.3 METHODS FOR MEASURING MOLECULAR MARKER DATA

The techniques described in this section are particularly useful for obtaining molecular marker data for step 202 wherein the data is reflective of the products of the molecular marker –e.g. measurement of the abundance of RNA or protein products in blood corresponding to all of the molecular markers of the genome or “a portion thereof”. In particular, the techniques useful for step 202 are those techniques which allow the ability to comprehensively screen for candidate molecular markers quickly and effectively. These techniques preferably provide molecular marker data for a large number of molecular markers concurrently, thereby allowing greater ability to screen molecular markers corresponding to the entire genome, or a portion thereof in a short period of time. In addition to the techniques described in this Section 5.3, any technique known to one of skill in the art to measure the abundance of RNA or protein corresponding to the entire genome or “a portion thereof” can be used to measure such data. In one embodiment, “a portion thereof” is data corresponding to the amount of RNA or protein expressed from more than 1,000, more than 2,000, more than 5,000, more than 10,000, more than 20,000, more than 30,000 molecular markers. In another embodiment, the “a portion thereof” refers to at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% of the genome. See, e.g., Sambrook, Fritsch & Maniatis, 1982, *Molecular Cloning: A Laboratory Manual*; *DNA Cloning: A Practical Approach*, volumes I and II (D.N. Glover ed. 1985); *Oligonucleotide Synthesis* Gait ed., 1984; *Nucleic Acid Hybridization*, Hames & Higgins eds., 1985; *Transcription and Translation*, Hames & Higgins eds., 1984, *Animal Cell Culture*, Freshney ed., 1986, *Immobilized Cells And Enzymes*, IRL Press, 1986, Perbal, 1984, *A Practical Guide To Molecular Cloning*, each of which is hereby incorporated by reference in its entirety. In one embodiment more than technique can be used to measure data for each molecular marker to perform step 202.

#### 5.3.1 RNA MEASUREMENT TECHNIQUES

Any technique known to one of skill in the art may be used to measure the level of expression of a molecular marker by measuring the amount of the product of the molecular

marker. In one embodiment the RNA in blood corresponding to the molecular marker is measured. By “corresponding to a molecular marker” is meant RNA transcribed from a molecular marker (or proteins translated from RNA which is transcribed from a molecular marker when referring to protein products of a molecular marker). RNA or protein which  
5 corresponds to a molecular marker are also considered the product of the molecular marker. In a specific embodiment, the level of an RNA product is measured using a technique which permits generation of data for a large number of molecular markers. However measured, the result is either the absolute or relative amounts of abundance of nucleic acids corresponding to the molecular markers, including but not limited to values  
10 representing abundances or abundance ratios.

### 5.3.1.1 MICROARRAYS

In one embodiment, nucleic acid arrays are employed for analyzing the level of RNA product of each molecular marker of the genome in a blood sample. In a specific embodiment, molecular marker data is obtained by hybridizing detectably labeled  
15 polynucleotides representing the nucleic acid sequences in mRNA transcripts present in a cell (*e.g.*, fluorescently labeled cDNA synthesized from total cell mRNA) to a microarray. In some embodiments expressed transcripts that may or may not represent genes expressed in the blood sample are analyzed.

In some embodiments, a microarray is an array of positionally-addressable binding  
20 (*e.g.*, hybridization) sites on a support for representing many of the nucleic acid sequences in the genome of a cell or organism. In some embodiments, a microarray represents most or almost all of the genes in a species. In some embodiments, each microarray binding site consists of polynucleotide probes bound to a predetermined region on the support. Microarrays are described in Draghici, *Data Analysis Tools For DNA Microarrays*, 2003, Chapman & Hall, CRC Press, New York, pp. 15-16, which is hereby incorporated by  
25 reference in its entirety.

Microarrays can be made in a number of ways. See, for example, Draghici, *Data Analysis Tools For DNA Microarrays*, 2003, Chapman & Hall, CRC Press, New York, pp. 16-22, which is hereby incorporated by reference in its entirety. Preferably microarrays are  
30 reproducible, allowing multiple copies of a given array to be produced and results from the microarrays compared with each other. Preferably, the microarrays are made from materials that are stable under binding (*e.g.*, nucleic acid hybridization) conditions. Microarrays are preferably small, *e.g.*, between 1 cm<sup>2</sup> and 25 cm<sup>2</sup>, preferably 1 to 3 cm<sup>2</sup>. However, both larger and smaller arrays are also contemplated and may be preferable, *e.g.*,

for simultaneously evaluating a very large number or very small number of different probes.

In some embodiments, a given binding site or unique set of binding sites in the microarray will specifically bind (*e.g.*, hybridize) to a nucleotide sequence in a single gene  
5 from a cell or organism (*e.g.*, to exon of a specific mRNA or a specific cDNA derived therefrom).

Microarrays used in the present invention can include one or more test probes. In some embodiments each such test probe comprises a polynucleotide sequence that is complementary to a subsequence of RNA or DNA to be detected. Each probe typically  
10 has a different nucleic acid sequence, and the position of each probe on the solid surface of the array is usually known or can be determined. Microarrays useful in accordance with the invention can include oligonucleotide microarrays, cDNA based arrays, SNP arrays, spliced variant arrays and any other array able to provide a quantitative or semi quantitative data of the invention. Some types of microarrays are addressable arrays.  
15 More specifically, some microarrays are positionally addressable arrays. In some embodiments, each probe of the array is located at a known, predetermined position on the solid support so that the identity (*e.g.*, the sequence) of each probe can be determined from its position on the array (*e.g.*, on the support or surface). In some embodiments, the arrays are ordered arrays.

In some embodiments, the density of probes on a microarray or a set of microarrays  
20 is 100 different (*e.g.*, non-identical) probes per 1 cm<sup>2</sup> or higher. More preferably, a microarray used in the methods of the invention will have at least 550 probes per 1 cm<sup>2</sup>, at least 1,000 probes per 1 cm<sup>2</sup>, at least 1,500 probes per 1 cm<sup>2</sup> or at least 2,000 probes per 1 cm<sup>2</sup>. In a particularly preferred embodiment, the microarray is a high density array,  
25 preferably having a density of at least 2,500 different probes per 1 cm<sup>2</sup>. The microarrays used in the invention therefore preferably contain at least 2,500, at least 5,000, at least 10,000, at least 15,000, at least 20,000, at least 25,000, at least 50,000 or at least 55,000 different (*i.e.*, non-identical) probes.

In one embodiment, the microarray is an array (*e.g.*, a matrix) in which each  
30 position represents a discrete binding site for a nucleotide sequence of a transcript encoded by a gene (*e.g.*, for an exon of an mRNA or a cDNA derived therefrom). The collection of binding sites on a microarray contains sets of binding sites for a plurality of genes and thus can be used, in some embodiments to measure molecular marker data. For example, in various embodiments, the microarrays of the invention can comprise binding sites for



products encoded by fewer than 50% of the genes in the genome of an organism.

Alternatively, the microarrays of the invention can have binding sites for the products encoded by at least 50%, at least 75%, at least 85%, at least 90%, at least 95%, at least 99% or 100% of the molecular markers of an organism. In other embodiments, the

5 microarrays of the invention can have binding sites for products encoded by fewer than 50%, by at least 50%, by at least 75%, by at least 85%, by at least 90%, by at least 95%, by at least 99% or by 100% of the genes expressed by a cell of an organism. The binding site can be a DNA or DNA analog to which a particular RNA can specifically hybridize. The DNA or DNA analog can be, e.g., a synthetic oligomer or a gene fragment, e.g.  
10 corresponding to an exon.

In some embodiments of the present invention, an expressed transcript is represented in the nucleic acid arrays. In such embodiments, a set of binding sites can include probes with different polynucleotides that are complementary to different sequence segments of the expressed transcript. Exemplary polynucleotides that fall within this class  
15 can be of length of 15 to 200 bases, 20 to 100 bases, 40-60 bases or some other range of bases. Each probe sequence can also comprise linker sequences in addition to the sequence that is complementary to its target sequence. As used herein, a linker sequence is a sequence between the sequence that is complementary to its target sequence and the surface of support. For example, in some embodiments, the nucleic acid arrays of the  
20 invention comprise one probe specific to each target gene or exon. However, if desired, the nucleic acid arrays can contain at least 2, 5, 10, 100, or 1000 or more probes specific to some expressed transcript. For example, the array may contain probes tiled across the sequence of the longest mRNA isoform of a gene at single base steps.

In specific embodiments of the invention, when an exon has alternative spliced  
25 variants, a set of polynucleotide probes of successive overlapping sequences, i.e., tiled sequences, across the genomic region containing the longest variant of an exon can be included in the exon nucleic acid arrays. The set of polynucleotide probes can comprise successive overlapping sequences at steps of a predetermined base intervals, e.g. at steps of 1, 5, or 10 base intervals, span, or are tiled across, the mRNA containing the longest  
30 variant. Such sets of probes therefore can be used to scan the genomic region containing all variants of an exon to determine the expressed variant or variants of the exon to determine the expressed variant or variants of the exon. Alternatively or additionally, a set of polynucleotide probes comprising exon specific probes and/or variant junction probes can be included in the exon profiling array. As used herein, a variant junction probe refers

to a probe specific to the junction region of the particular exon variant and the neighboring exon. In some cases, the probe set contains variant junction probes specifically hybridizable to each of all different splice junction sequences of the exon. In other cases, the probe set contains exon specific probes specifically hybridizable to the common sequences in all different variants of the exon, and/or variant junction probes specifically hybridizable to the different splice junction sequences of the exon.

In some cases, an exon is represented in the exon nucleic acid arrays by a probe comprising a polynucleotide that is complementary to the full length exon. In such instances, an exon is represented by a single binding site on the profiling arrays. In some preferred cases, an exon is represented by one or more binding sites on the profiling arrays, each of the binding sites comprising a probe with a polynucleotide sequence that is complementary to an RNA fragment that is a substantial portion of the target exon. The lengths of such probes are normally between 15-600 bases, preferably between 20-200 bases, more preferably between 30-100 bases, and most preferably between 40-80 bases. The average length of an exon is 200 bases (see, e.g., Lewin, Genes V, Oxford University Press, Oxford, 1994). A probe of length of 40-80 allows more specific binding of the exon than a probe of shorter length, thereby increasing the specificity of the probe to the target exon. For certain genes, one or more targeted exons may have sequence lengths less than 40-80 bases. In such cases, if probes with sequences longer than the target exons are to be used, it may be desirable to design probes comprising sequences that include the entire target exon flanked by sequences from the adjacent constitutively splice exon or exons such that the probe sequences are complementary to the corresponding sequence segments in the mRNAs. Using flanking sequence from adjacent constitutively spliced exon or exons rather than the genomic flanking sequences, i.e., intron sequences, permits comparable hybridization stringency with other probes of the same length. Preferably the flanking sequence used are from the adjacent constitutively spliced exon or exons that are not involved in any alternative pathways. More preferably the flanking sequences used do not comprise a significant portion of the sequence of the adjacent exon or exons so that cross-hybridization can be minimized. In some embodiments, when a target exon that is shorter than the desired probe length is involved in alternative splicing, probes comprising flanking sequences in different alternatively spliced mRNAs are designed so that expression level of the exon expressed in different alternatively spliced mRNAs can be measured.

In some instances, when alternative splicing pathways and/or exon duplication in separate genes are to be distinguished, the DNA array or set of arrays can also comprise probes that are complementary to sequences spanning the junction regions of two adjacent exons. Preferably, such probes comprise sequences from the two exons which are not substantially overlapped with probes for each individual exons so that cross hybridization can be minimized. Probes that comprise sequences from more than one exons are useful in distinguishing alternative splicing pathways and/or expression of duplicated exons in separate genes if the exons occurs in one or more alternative spliced mRNAs and/or one or more separated genes that contain the duplicated exons but not in other alternatively spliced mRNAs and/or other genes that contain the duplicated exons. Alternatively, for duplicate exons in separate genes, if the exons from different genes show substantial difference in sequence homology, it is preferable to include probes that are different so that the exons from different genes can be distinguished.

It will be apparent to one skilled in the art that any of the probe schemes, supra, can be combined on the same nucleic acid array and/or on different arrays within the same set of nucleic acid arrays so that a more accurate determination of the expression profile for a plurality of molecular marker products can be accomplished. It will also be apparent to one skilled in the art that the different probe schemes can also be used for different levels of accuracies in profiling. For example, a nucleic acid array or array set comprising a small set of probes for each expressed transcript or each region thereof may be used to identify molecular markers under certain specific conditions. An array or array set comprising larger sets of probes for the exons that are of interest is then used to more accurately determine the specific molecular marker products under such specific conditions. Other DNA array strategies that allow more advantageous use of different probe schemes are also encompassed.

In some embodiments, the microarrays used in the invention can include binding sites (*e.g.*, probes) for sets of exons for one or more genes relevant to the condition of interest. The number of genes in a genome can be estimated from the number of mRNAs expressed by the cell or organism, or by extrapolation of a well characterized portion of the genome. When the genome of the organism of interest has been sequenced, the number of ORFs can be determined and mRNA coding regions identified by analysis of the DNA sequence. For example, the human genome is now known. Genome sequences for other organisms are also completed or nearly completed. Thus, in some embodiments of the invention, an array set comprising the total probes for all known or predicted exons

in the genome of an organism is provided. As a non-limiting example, the present invention provides an array set comprising one or two probes for each known or predicted exon of a molecular marker of the human genome.

It will be appreciated that when cDNA complementary to the RNA of a cell is made and hybridized to a microarray under suitable hybridization conditions, the level of hybridization to the site in the array corresponding to an exon of any particular molecular marker will reflect the prevalence in the cell of mRNA or mRNAs containing the exon transcribed from that molecular marker. For example, when detectably labeled (*e.g.*, with a fluorophore) cDNA complementary to the total cellular mRNA is hybridized to a microarray, the site on the array corresponding to an exon of a gene (*i.e.*, capable of specifically binding the product or products of the gene expressing) that is not transcribed or is removed during RNA splicing in the cell will have little or no signal (*e.g.*, fluorescent signal), and an exon of a gene for which the encoded mRNA expressing the exon is prevalent will have a relatively strong signal. The relative abundance of different mRNAs produced from the same gene by alternative splicing is then determined by the signal strength pattern across the whole set of exons monitored for the gene.

The use of a two-color fluorescence labeling and detection scheme to define alterations in gene expression has been described in connection with detection of mRNAs, *e.g.*, in Shena *et al.*, 1995, Science 270:467-470, which is incorporated by reference in its entirety for all purposes. In some embodiments, such schemes are used to measure molecular marker data. Such schemes are equally applicable to labeling and detection of expressed transcripts. An advantage of using cDNA labeled with two different fluorophores is that a direct and internally controlled comparison of the mRNA or exon expression levels corresponding to each arrayed gene in two blood samples can be made, and variations due to minor differences in experimental conditions (*e.g.*, hybridization conditions) will not affect subsequent analyses. However, it will be recognized that it is also possible to use cDNA from a single cell, and compare, for example, the absolute amount of a particular exon in, *e.g.*, a drug-treated or pathway-perturbed cell and an untreated cell. Furthermore, labeling with more than two colors is also contemplated in the present invention. In some embodiments of the invention, at least 5, 10, 20, or 100 dyes of different colors can be used for labeling. Such labeling permits simultaneous hybridizing of the distinguishably labeled cDNA populations to the same array, and thus measuring, and optionally comparing the expression levels of, mRNA molecules derived from more than two samples. Dyes that can be used include, but are not limited to,

fluorescein and its derivatives, rhodamine and its derivatives, texas red, 5' carboxy-fluorescein ("FMA"), 2',7'-dimethoxy-4',5'-dichloro-6-carboxy-fluorescein ("JOE"), N,N,N',N'-tetramethyl-6-carboxy-rhodamine ("TAMRA"), 6' carboxy-X-rhodamine ("ROX"), HEX, TET, IRD40, and IRD41, cyamine dyes, including but are not limited to  
5 Cy3, Cy3.5 and Cy5; BODIPY dyes including but are not limited to BODIPY-FL, BODIPY-TR, BODIPY-TMR, BODIPY-630/650, and BODIPY-650/670; and ALEXA dyes, including but are not limited to ALEXA-488, ALEXA-532, ALEXA-546, ALEXA-568, and ALEXA-594; as well as other fluorescent dyes which will be known to those who are skilled in the art.

10 In one embodiment, hybridization levels at different hybridization times are measured separately on different, identical microarrays. For each such measurement, at hybridization time when hybridization level is measured, the microarray is washed briefly, preferably in room temperature in an aqueous solution of high to moderate salt concentration (e.g., 0.5 to 3 M salt concentration) under conditions which retain all bound  
15 or hybridized polynucleotides while removing all unbound polynucleotides. The detectable label on the remaining, hybridized polynucleotide molecules on each probe is then measured by a method which is appropriate to the particular labeling method used. The resulted hybridization levels are then combined to form a hybridization curve. In another embodiment, hybridization levels are measured in real time using a single  
20 microarray. In this embodiment, the microarray is allowed to hybridize to the sample without interruption and the microarray is interrogated at each hybridization time in a non-invasive manner. In still another embodiment, one can use one array, hybridize for a short time, wash and measure the hybridization level, put back to the same sample, hybridize for another period of time, wash and measure again to get the hybridization time curve.

25 In a specific embodiment, the Affymetrix® Human Genome U133 (HG-U133) Set, consisting of two GeneChip® arrays, is used in accordance with known methods. The Human Genome U133 (HG-U133) Set contains almost 45,000 probe sets representing more than 39,000 transcripts derived from approximately 33,000 well-substantiated human genes. This set design uses sequences selected from GenBank®, dbEST, and RefSeq. The  
30 sequence clusters were created from the UniGene database (Build 133, April 20, 2001). They were then refined by analysis and comparison with a number of other publicly available databases including the Washington University EST trace repository and the University of California, Santa Cruz Golden Path human genome database (April 2001 release).

In another embodiment, the HG-U133A array is used in accordance with the methods of the invention. The HG-U133A array includes representation of the RefSeq database sequences and probe sets related to sequences previously represented on the Human Genome U95Av2 array. The HG-U133B array contains primarily probe sets  
5 representing EST clusters. In another embodiment, the U133 Plus 2.0 GeneChip® is used in the invention. The U133 Plus 2.0 GeneChip® represents over 47,000 transcripts.

In another embodiment, a cDNA based microarray is used. In one embodiment the ChondroChip™ is used in accordance with the methods of the invention. The ChondroChip™ is a cDNA based microarray. One version of the ChondroChip™ includes  
10 14,976 distinct elements: 10,382 known genes (69%), 4,112 EST/genomic DNA matches (28%), 328 clones with no significant match (2.2%), and 154 control spots (1.0%). Most if not all of the elements on the ChondroChip™ are complementary to ESTs identified as expressed in human chondrocytes. An article that describes the creation of a version of the ChondroChip™ is Zhang *et al.*, 2002, Osteoarthritis and Cartilage 10, 950-960, which is  
15 hereby incorporated by reference in its entirety.

In another embodiment, the BloodChip™ is used in accordance with the methods of the invention. The BloodChip is a cDNA microarray slide with 10,368 PCR products derived from peripheral blood cell cDNA libraries. The creation of the BloodChip™ microarray is described in Ma and Liew, 2003, Journal of Molecular and Cellular  
20 Cardiology 8, 993-998, which is hereby incorporated by reference in its entirety.

#### **5.3.1.2 TARGET POLYNUCLEOTIDE MOLECULES**

Target polynucleotides that can be analyzed by the methods and compositions of the invention include RNA molecules such as, but by no means limited to, expressed RNA molecules which includes messenger RNA (mRNA) molecules, mRNA spliced variants as  
25 well as other regulatory RNA, cRNA molecules (e.g., RNA molecules prepared from cDNA molecules that are transcribed in vivo) and fragments thereof. Target polynucleotides which may also be analyzed by the methods and compositions of the present invention include, but are not limited to DNA molecules such as genomic DNA molecules, cDNA molecules, and fragments thereof including oligonucleotides, ESTs,  
30 STSs, etc

The target polynucleotide molecules may be naturally occurring nucleic acid molecules such as genomic or extragenomic DNA molecules isolated from a blood sample, or RNA molecules, such as mRNA molecules, isolated from a blood sample. The sample of target polynucleotides can comprise, e.g., molecules of DNA, RNA, or copolymers of

DNA and RNA. In specific embodiments, the target polynucleotides of the invention will correspond to particular genes or to particular gene transcripts (e.g., to particular mRNA sequences expressed in specific cell types or to particular cDNA sequences derived from such mRNA sequences). The target polynucleotides may correspond to different exons of  
5 the same gene, e.g., so that different splice variants of that gene may be detected and/or analyzed.

In specific embodiments, the target polynucleotides to be analyzed are prepared in vitro from nucleic acids extracted from a blood sample. For example, in one embodiment, RNA is extracted from a blood sample (e.g., total cellular RNA, poly(A)+ messenger  
10 RNA, fraction thereof) and messenger RNA is purified from the total extracted RNA. Methods for preparing total and poly(A)+ RNA are well known in the art, and are described generally, e.g., in Sambrook, Fritsch & Maniatis, "Molecular Cloning: A Laboratory Manual (1982); "DNA Cloning: A Practical Approach," Volumes I and II (D.N. Glover ed. 1985). In one embodiment, RNA is extracted from a blood sample using  
15 guanidinium thiocyanate lysis followed by CsCl centrifugation and an oligo dT purification (Chirgwin et al., 1979, Biochemistry 18:5294-5299). In another embodiment, RNA is extracted from a blood sample using guanidinium thiocyanate lysis followed by purification on RNeasy columns (Qiagen). cDNA is then synthesized from the purified mRNA using, e.g., oligo-dT or random primers. In specific embodiments, the target  
20 polynucleotides are cRNA prepared from purified messenger RNA extracted from a blood sample. As used herein, cRNA is defined here as RNA complementary to the source RNA. The extracted RNAs can be amplified using a process in which doubled-stranded cDNAs are synthesized from the RNAs using a primer linked to an RNA polymerase promoter in a direction capable of directing transcription of anti-sense RNA. Anti-sense  
25 RNAs or cRNAs are then transcribed from the second strand of the double-stranded cDNAs using an RNA polymerase (see, e.g., U.S. Patent Nos. 5,891,636, 5,716,785; 5,545,522 and 6,132,997; see also, U.S. Patent No. 6,271,002, and U.S. Provisional Patent Application Serial No. 60/253,641, filed on November 28, 2000, by Ziman et al.). Both  
30 oligo-dT primers (U.S. Patent Nos. 5,545,522 and 6,132,997) or random primers (U.S. Provisional Patent Application Serial No. 60/253,641, filed on November 28, 2000, by Ziman et al.) that contain an RNA polymerase promoter or complement thereof can be used. In some embodiments the target polynucleotides are short and/or fragmented polynucleotide molecules which are representative of the original nucleic acid population of the blood sample.

The target polynucleotides to be analyzed by the methods and compositions of the invention can be detectably labeled. For example, cDNA can be labeled directly, *e.g.*, with nucleotide analogs, or indirectly, *e.g.*, by making a second, labeled cDNA strand using the first strand as a template. Alternatively, the double-stranded cDNA can be transcribed into cRNA and labeled.

In some embodiments the detectable label is a fluorescent label, *e.g.*, by incorporation of nucleotide analogs. Other labels suitable for use in the present invention include, but are not limited to, biotin, imminobiotin, antigens, cofactors, dinitrophenol, lipoic acid, olefinic compounds, detectable polypeptides, electron rich molecules, enzymes capable of generating a detectable signal by action upon a substrate, and radioactive isotopes. Suitable radioactive isotopes include  $^{32}\text{P}$ ,  $^{35}\text{S}$ ,  $^{14}\text{C}$ ,  $^{15}\text{N}$  and  $^{125}\text{I}$ . Fluorescent molecules suitable for the present invention include, but are not limited to, fluorescein and its derivatives, rhodamine and its derivatives, texas red, 5'-carboxy-fluorescein ("FMA"), 2',7'-dimethoxy-4',5'-dichloro-6-carboxy-fluorescein ("JOE"), N,N,N',N'-tetramethyl-6-carboxy-rhodamine ("TAMRA"), 6'-carboxy-X-rhodamine ("ROX"), HEX, TET, IRD40, and IRD41. Fluorescent molecules that are suitable for the invention further include: cyanine dyes, including but not limited to Cy3, Cy3.5 and Cy5; BODIPY dyes including but not limited to BODIPY-FL, BODIPY-TR, BODIPY-TMR, BODIPY-630/650, and BODIPY-650/670; and ALEXA dyes, including but not limited to ALEXA-488, ALEXA-532, ALEXA-546, ALEXA-568, and ALEXA-594; as well as other fluorescent dyes which will be known to those who are skilled in the art. Electron rich indicator molecules suitable for the present invention include, but are not limited to, ferritin, hemocyanin, and colloidal gold. Alternatively, in some embodiments the target polynucleotides may be labeled by specifically complexing a first group to the polynucleotide. A second group, covalently linked to an indicator molecule and which has an affinity for the first group, can be used to indirectly detect the target polynucleotide. In such an embodiment, compounds suitable for use as a first group include, but are not limited to, biotin and iminobiotin. Compounds suitable for use as a second group include, but are not limited to, avidin and streptavidin.

In a specific embodiment, the target polynucleotides are prepared as follows: 2  $\mu\text{g}$  Oligo-dT primers are annealed to 2  $\mu\text{g}$  of mRNA isolated from a blood sample of a patient in a total volume of 15  $\mu\text{l}$ , by heating to 70°C for 10 min, and cooled on ice. The mRNA is reverse transcribed by incubating the sample at 42°C for 1.5-2 hours in a 100  $\mu\text{l}$  volume containing a final concentration of 50mM Tris-HCl (pH 8.3), 75mM KCl, 3mM  $\text{MgCl}_2$ ,



25mM DTT, 25mM unlabeled dNTPs, 400 units of Superscript II (200U/μL, Gibco BRL), and 15mM of Cy3 or Cy5 (Amersham). RNA is then degraded by addition of 15μl of 0.1N NaOH, and incubation at 70°C for 10 min. The reaction mixture is neutralized by addition of 15μl of 0.1N HCl, and the volume is brought to 500μl with TE (10mM Tris, 1mM EDTA), and 20 μg of Cot1 human DNA (Gibco-BRL) is added.

The labeled target polynucleotide molecules are purified by centrifugation in a Centricon-30 micro-concentrator (Amicon). If two different target polynucleotide samples (e.g., two samples derived from a healthy patient vs. patient with a disease) are being analyzed and compared by hybridization to the same array, each target nucleic acid sample is labeled with a different fluorescent label (e.g., Cy3 and Cy5) and separately concentrated. The separately concentrated target nucleic acid samples (Cy3 and Cy5 labeled) are combined into a fresh centricon, washed with 500μl TE, and concentrated again to a volume of less than 7μl. 1μL of 10μg/μl polyA RNA (Sigma, #P9403) and 1μl of 10μg/μl tRNA (Gibco-BRL, #15401-011) is added and the volume is adjusted to 9.5μl with distilled water. For final target polynucleotide preparation 2.1μl 20XSSC (1.5M NaCl, 150mM NaCitrate (pH8.0)) and 0.35μl 10%SDS is added.

### 5.3.1.3 HYBRIDIZATION TO MICROARRAYS

In some embodiments, nucleic acid hybridization and wash conditions are chosen so that the polynucleotide molecules to be analyzed by the invention (e.g., “target polynucleotide molecules) specifically bind or specifically hybridize to the complementary polynucleotide sequences of the array, typically to a specific array site, where its complementary DNA is located.

Arrays containing double-stranded probe DNA situated thereon can be subjected to denaturing conditions to render the DNA single-stranded prior to contacting with the target polynucleotide molecules. Arrays containing single-stranded probe DNA (e.g., synthetic oligodeoxyribonucleic acids) may need to be denatured prior to contacting with the target polynucleotide molecules, e.g., to remove hairpins or dimers which form due to self complementary sequences.

Optimal hybridization conditions will depend on the length (e.g., oligomer versus polynucleotide greater than 200 bases) and type (e.g., RNA, or DNA) of probe and target nucleic acids. General parameters for specific (i.e., stringent) hybridization conditions for nucleic acids are described in Sambrook *et al.*, (*supra*), and in Ausubel *et al.*, 1987, *Current Protocols in Molecular Biology*, Greene Publishing and Wiley-Interscience, New York. When the cDNA microarrays of Schena *et al.* are used, typical hybridization

conditions are hybridization in 5 X SSC plus 0.2% SDS at 65 °C for four hours, followed by washes at 25°C in low stringency wash buffer (1 X SSC plus 0.2% SDS), followed by 10 minutes at 25°C in higher stringency wash buffer (0.1 X SSC plus 0.2% SDS) (Shena *et al.*, 1996, *Proc. Natl. Acad. Sci. U.S.A.* 93:10614). Useful hybridization conditions are also provided in, *e.g.*, Tijessen, 1993, *Hybridization With Nucleic Acid Probes*, Elsevier Science Publishers B.V. and Kricka, 1992, *Nonisotopic DNA Probe Techniques*, Academic Press, San Diego, CA.

Representative hybridization conditions for use with the screening and/or signaling chips in accordance with some embodiments of the present invention include hybridization at a temperature at or near the mean melting temperature of the probes (*e.g.*, within 5 °C, more typically within 2 °C) in 1 M NaCl, 50 mM MES buffer (pH 6.5), 0.5% sodium Sarcosine and 30% formamide.

In a specific embodiment, a labeled target polynucleotide molecules are denatured by heating for two minutes at 100°C, and incubated at 37°C for 20-30 min before being placed on a nucleic acid array under a 22mm x 22mm glass cover slip. Hybridization is carried out at 65°C for fourteen to eighteen hours in a custom slide chamber with humidity maintained by a small reservoir of 3XSSC. The array is washed by submersion and agitation for between two and five minutes in 2X SSC with 0.1%SDS, followed by 1X SSC, and 0.1X SSC. Finally, the array is dried by centrifugation for 2 min in a slide rack in a Beckman GS-6 tabletop centrifuge in Microplus carriers at 650 RPM for two minutes.

#### 5.3.1.4 SIGNAL DETECTION AND DATA ANALYSIS

It will be appreciated that when target sequences, *e.g.*, cDNA or cRNA, complementary to the RNA of a blood sample is made and hybridized to a microarray under suitable hybridization conditions, the level of hybridization to the site in the array corresponding to an exon of any particular gene will reflect the prevalence in the cell of mRNA or mRNAs containing the exon transcribed from that gene. For example, when detectably labeled (*e.g.*, with a fluorophore) cDNA complementary to the total cellular mRNA is hybridized to a microarray, the site on the array corresponding to an exon of a gene (*i.e.*, capable of specifically binding the product or products of the gene expressing) that is not transcribed or is removed during RNA splicing in the cell will have little or no signal (*e.g.*, fluorescent signal), and an exon of a gene for which the encoded mRNA expressing the exon is prevalent will have a relatively strong signal. The relative abundance of different mRNAs produced from the same gene by alternative splicing is

then determined by the signal strength pattern across the whole set of exons monitored for the gene.

Generally, any form of image processing may be used to digitize the microarrays and thereby obtain high throughput data for molecular markers in the present invention.

5 For example, any of the image processing techniques described or referenced in Draghici, *Data Analysis Tools For DNA Microarrays*, 2003, Chapman & Hall, CRC Press, New York, pp. 33-58, which is hereby incorporated by reference in its entirety, can be used. In some embodiments, two-color fluorescence is used. The use of a two-color fluorescence labeling and detection scheme to define alterations in gene expression has been described

10 in connection with detection of mRNAs, *e.g.*, in Shena *et al.*, 1995, *Science* 270:467-470, which is hereby incorporated by reference in its entirety for all purposes. The scheme is equally applicable to labeling and detection of exons. An advantage of using target sequences, *e.g.*, cDNAs or cRNAs, labeled with two different fluorophores is that a direct and internally controlled comparison of the mRNA or exon expression levels

15 corresponding to each arrayed gene in two states can be made, and variations due to minor differences in experimental conditions (*e.g.*, hybridization conditions) will not affect subsequent analyses.

In a specific embodiment, the labeled probes are scanned using a GMS Scanner 418 and Scanalyzer software (Michael Eisen, Stamford University), followed by

20 GeneSpring software (Silicon Genetics, CA) analysis. In another embodiment, a GMS Scanner 428 and Jaguar software are used followed by GeneSpring software analysis. In some embodiments a normalization routine, such as any of the normalization routines described in Section 5.7, is used.

### 5.3.2 RT-PCR AND QUANTITATIVE RT-PCR

25 In one aspect of the invention, the abundance or level of expression of an RNA product of a molecular marker can be measured performing reverse transcription on the RNA from blood and subsequently amplifying the resulting product ("RT-PCR"). In another embodiment, the abundance or level of expression of RNA can be measured from a blood sample by using quantitative RT-PCR or real time PCR ("QRT-PCR") on cDNA

30 copy of RNA. Total RNA, or mRNA from a blood sample can be used as a template and a primer specific to the transcribed portion of a gene of the invention is used to initiate reverse transcription. Methods of reverse transcribing RNA into cDNA are well known and described in, for example, Sambrook *et al.*, 1989, *supra*. Primer design can be accomplished utilizing commercially available software (*e.g.*, Primer Designer 1.0,

academic software, etc.). The product of the reverse transcription is subsequently used as a template for PCR. In one embodiment, a one step process can be used for either the RT-PCR and/or the QRT-PCR (combining the reverse transcription and PCR in a single reaction). In another embodiment, a two step process can be used for either the RT-PCR and/or the QRT-PCR (first doing the reverse transcription step and subsequently performing the PCR). In some embodiments, oligo(dT)-primed first strand cDNA synthesis is performed so as to specifically target the mRNA population (e.g. using the Applied Biosystems High Capacity cDNA Archive Kit (cat # 4322171), on a Perkin-Elmer DNA Thermal Cycler.

For quantitative RT-PCR, in some embodiments the reportable value is the Ct-value, which is the threshold cycle at which PCR is in the logarithmic phase. For each gene of interest in each RNA sample, a  $\Delta Ct$  value can be calculated by the formula:  $\Delta Ct = (Ct, \text{target gene}) - (Ct, \beta\text{-actin})$ . The  $\Delta Ct$  values from different groups of RNA samples can then be compared by the Mann-Whitney Rank Sum test.

In some embodiments, Quantitative RT-PCR can be done using probes including Taqman® probes (Perkin Elmer, Foster City, California). The probe is specific for the PCR product and has both a quencher and fluorescent reporter attached to the probe. Different fluorescent markers can be utilized. In some embodiments, multiple probes can be used in the quantitative RT-PCR process to allow for multiplexing reactions (e.g. allow for measurement of two molecular markers in one reaction well or container). When using TaqMan® probes, Taq DNA polymerase is used which has 5'-to-3' exonuclease activity and thus will cleave of the fluorescent reporter of the probe, freeing the fluorescent molecular from the quencher molecule. Thus the emission of fluorescence is used to measure the amount of PCR product being made. Other probes are also useful for quantitative RT-PCR including Molecular Beacons®.

Other known techniques for quantitative Rt-PCR is to use an intercalating dye such as the commercially available QuantiTect™ SYBR® Green PCR (Qiagen, Valencia California).

Additionally, other systems to quantitatively measure mRNA expression products are known including Scorpions® (Zeneca Limited) or Fluorescent Polarization Probes (see e.g. *Zeneca Limited, 6,007,984*) etc.

### 5.3.3 NUCLEASE PROTECTION ASSAYS

Nuclease protection assays (including both ribonuclease protection assays and S1 nuclease assays) can be used to detect and quantify specific products of molecular

markers. In nuclease protection assays, an antisense probe (labeled with, e.g., radiolabeled or nonisotopic) hybridizes in solution to an RNA sample. Following hybridization, single-stranded, unhybridized probe and RNA are degraded by nucleases. An acrylamide gel is used to separate the remaining protected fragments. Typically, solution hybridization is more efficient than membrane-based hybridization, and it can accommodate up to 100 µg of sample RNA, compared with the 20-30 µg maximum of blot hybridizations.

The ribonuclease protection assay, which is the most common type of nuclease protection assay, requires the use of RNA probes. Oligonucleotides and other single-stranded DNA probes can only be used in assays containing S1 nuclease. The single-stranded, antisense probe must typically be completely homologous to target RNA to prevent cleavage of the probe:target hybrid by nuclease.

#### 5.3.4 MASS SPECTROMETRY

Mass spectrometry (e.g., electrospray ionization “ESI”, matrix-assisted laser desorption-ionization “MALDI”, and Fourier-transform ion cyclotron resonance “FT-ICR”) can be used to measure data (e.g., mass, charge) of molecular markers in blood samples. Such molecular markers that can be characterized by mass spectrometry include but are not limited to, proteins, nucleic acids, carbohydrates, and other biological macromolecules. This section provides brief and non-limiting examples of mass spectrometry techniques that can be used to quantitatively characterize molecular markers.

MALDI uses a pulsed laser for desorption of the ions and a time-of-flight analyzer and has been used for the detection of noncovalent tRNA:amino-acyl-tRNA synthetase complexes. See, for example, Gruic-Sovulj et al., 1997, *J. Biol. Chem.* 272:32084. ESI mass spectrometry (“ESI-MS”) has been used for studying non-covalent molecular interactions. ESI-MS generates molecular ions with little to no fragmentation. See, for example, Xavier et al., 2000, *Trends Biotechnol.* 18:349. Fourier-transform ion cyclotron resonance (“FT-ICR”) mass spectrometry provides high-resolution spectra, isotope-resolved precursor ion selection, and accurate mass assignments. See, for example, Xavier et al., 2000, *Trends Biotechnol.* 18:349.

Tandem mass spectrometry is described in Link et al., 1999, *Nat. Biotechnol.* 17, 676-682; Washburn et al. 2001, *Nat. Biotechnol.* 19, 242; Gaven et al., 2002, *Nature* 415, 141; and Ho et al., 2002, *Nature* 418, 180). In the case of proteins from a blood sample, the proteins can first be digested into peptides using an enzyme such as trypsin and then subjected to liquid chromatography tandem mass spectrometry (MS/MS). Liquid chromatography provides an initial separation of the peptides, which are then ionized

directly into a mass spectrometer. Following an initial scan in which the mass/charge ratio of all intact (parent) ions from the peptides are measured, the mass spectrometer selects a parent ion, fragments it and obtains the mass spectrum of the generated fragments. These fragmentation patterns are called tandem mass spectra or MS/MS spectra. This process of ion selection and fragmentation is repeated throughout the liquid chromatography separation, thus generating a set of time resolved MS/MS spectra, with each spectrum representing a species eluting at a particular time from the LC separation. The resolving power of the liquid chromatography step, combined with the high mass resolution of modern mass spectrometers typically assures that each MS/MS spectrum represents the fragmentation pattern of a unique peptide in the digest.

### **5.3.5 COMPARATIVE GENE EXPRESSION PROFILING**

In some embodiments of the present invention quantitative measurement of molecular marker data is performed using comparative gene-expression profiling. An example of such technology is the multiplex microsphere bead assay used by Fuja et al., 2004, Journal of Biotechnology 108, 193,.

### **5.3.6 TRANSCRIPTION BASED AMPLIFICATION SYSTEMS**

In another aspect of the invention, the level of expression of a molecular marker in blood can be measured by amplifying RNA from a blood sample using transcription based amplification systems (TAS), including nucleic acid sequence amplification (NASBA) and 3SR. See, e.g., Kwoh et al., 1989, PNAS USA 86:1173; International Publication No. WO 88/10315; and U.S. Patent No. 6,329,179. In NASBA, the nucleic acids can be prepared for amplification using conventional phenol/chloroform extraction, heat denaturation, treatment with lysis buffer and minispin columns for isolation of DNA and RNA or guanidinium chloride extraction of RNA. These amplification techniques involve annealing a primer that has target specific sequences. Following polymerization, DNA/RNA hybrids are digested with RNase H while double stranded DNA molecules are heat denatured again. In either case, the single stranded DNA is made fully double stranded by addition of second target specific primer, followed by polymerization. The double-stranded DNA molecules are then multiply transcribed by a polymerase such as T7 or SP6. In an isothermal cyclic reaction, the RNA's are reverse transcribed into double stranded DNA, and transcribed once with a polymerase such as T7 or SP6. The resulting products, whether truncated or complete, indicate target specific sequences.

### 5.3.7 ADDITIONAL TECHNIQUES FOR DETECTING AND QUANTIFYING RNA

Many other techniques are known to one of skill for detecting and measuring RNA and can be used in accordance with the methods of the invention. Non-limiting examples of such techniques include Northern blotting, nuclease protection assays, RNA fingerprinting, polymerase chain reaction, ligase chain reaction, Qbeta replicase, isothermal amplification method, strand displacement amplification, transcription based amplification systems, nuclease protection (SI nuclease or RNase protection assays) as well as methods disclosed in International Publication Nos. WO 88/10315 and WO 89/06700, and International Applications Nos. PCT/US87/00880 and PCT/US89/01025.

A standard Northern blot assay can be used to ascertain an RNA transcript size, identify alternatively spliced RNA transcripts, and the relative amounts of mRNA in a blood sample, in accordance with conventional Northern hybridization techniques known to those persons of ordinary skill in the art. In Northern blots, RNA samples are first separated by size via electrophoresis in an agarose gel under denaturing conditions. The RNA is then transferred to a membrane, crosslinked and hybridized with a labeled probe. Nonisotopic or high specific activity radiolabeled probes can be used including random-primed, nick-translated, or PCR-generated DNA probes, in vitro transcribed RNA probes, and oligonucleotides. Additionally, sequences with only partial homology (e.g., cDNA from a different species or genomic DNA fragments that might contain an exon) may be used as probes. The labeled probe, e.g., a radiolabelled cDNA, either containing the full-length, single stranded DNA or a fragment of that DNA sequence may be at least 20, at least 30, at least 50, or at least 100 consecutive nucleotides in length. The probe can be labeled by any of the many different methods known to those skilled in this art. The labels most commonly employed for these studies are radioactive elements, enzymes, chemicals that fluoresce when exposed to ultraviolet light, and others. A number of fluorescent materials are known and can be utilized as labels. These include, but are not limited to, fluorescein, rhodamine, auramine, Texas Red, AMCA blue and Lucifer Yellow. A particular detecting material is anti-rabbit antibody prepared in goats and conjugated with fluorescein through an isothiocyanate. Proteins can also be labeled with a radioactive element or with an enzyme. The radioactive label can be detected by any of the currently available counting procedures. Non-limiting examples of isotopes include  $^3\text{H}$ ,  $^{14}\text{C}$ ,  $^{32}\text{P}$ ,  $^{35}\text{S}$ ,  $^{36}\text{Cl}$ ,  $^{51}\text{Cr}$ ,  $^{57}\text{Co}$ ,  $^{58}\text{Co}$ ,  $^{59}\text{Fe}$ ,  $^{90}\text{Y}$ ,  $^{125}\text{I}$ ,  $^{131}\text{I}$ , and  $^{186}\text{Re}$ . Enzyme labels are

likewise useful, and can be detected by any of the presently utilized colorimetric, spectrophotometric, fluorospectrophotometric, amperometric or gasometric techniques. The enzyme is conjugated to the selected particle by reaction with bridging molecules such as carbodiimides, diisocyanates, glutaraldehyde and the like. Any enzymes known to one of skill in the art can be utilized. Examples of such enzymes include, but are not limited to, peroxidase, beta-D-galactosidase, urease, glucose oxidase plus peroxidase and alkaline phosphatase. U.S. Patent Nos. 3,654,090, 3,850,752, and 4,016,043 are referred to by way of example for their disclosure of alternate labeling material and methods.

Nuclease protection assays (including both ribonuclease protection assays and S1 nuclease assays) can be used to detect and quantitate specific mRNAs. In nuclease protection assays, an antisense probe (labeled with, e.g., radiolabeled or nonisotopic) hybridizes in solution to an RNA sample. Following hybridization, single-stranded, unhybridized probe and RNA are degraded by nucleases. An acrylamide gel is used to separate the remaining protected fragments. Typically, solution hybridization is more efficient than membrane-based hybridization, and it can accommodate up to 100 µg of sample RNA, compared with the 20-30 µg maximum of blot hybridizations.

The ribonuclease protection assay, which is the most common type of nuclease protection assay, requires the use of RNA probes. Oligonucleotides and other single-stranded DNA probes can only be used in assays containing S1 nuclease. The single-stranded, antisense probe must typically be completely homologous to target RNA to prevent cleavage of the probe:target hybrid by nuclease.

Additional techniques to quantitatively measure RNA expression include, but are not limited to, ligase chain reaction, Qbeta replicase (see, e.g., International Application No. PCT/US87/00880), isothermal amplification method (see, e.g., Walker et al., 1992, PNAS 89:382-396), strand displacement amplification (SDA), repair chain reaction, Asymmetric Quantitative PCR (see, e.g., U.S. Publication No. US200330134307A1) and the multiplex microsphere bead assay described in Fuja et al., 2004, Journal of Biotechnology 108:193-205.

#### **5.3.7.1 SEPARATION OF AMPLIFICATION PRODUCTS**

Some of the quantitative measurement techniques described above may require separation of amplification products. Several techniques can be used to separate such amplification products. For example, amplification products can be separated by agarose, agarose-acrylamide or polyacrylamide gel electrophoresis using conventional methods. Several techniques for detecting PCR products quantitatively without electrophoresis can



also be used according to the invention. See, for example, *CR Protocols, A Guide to Methods and Applications*, Innis *et al.*, Academic Press, Inc. N.Y., 1990). For example, chromatographic techniques can be employed to effect separation. There are many kinds of chromatography that can be used in the present invention: adsorption, partition, ion-exchange and molecular sieve, HPLC, and many specialized techniques for using them including column, paper, thin-layer and gas chromatography (Freifelder, *Physical Biochemistry Applications to Biochemistry and Molecular Biology*, 2nd ed., Wm. Freeman and Co., New York, N.Y., 1982).

Another example of a separation methodology is done by covalently labeling the oligonucleotide primers used in a PCR reaction with various types of small molecule ligands. In one such separation, a different ligand is present on each oligonucleotide. A molecule, perhaps an antibody or avidin if the ligand is biotin, that specifically binds to one of the ligands is used to coat the surface of a plate such as a 96 well ELISA plate. Upon application of the PCR reactions to the surface of such a prepared plate, the PCR products are bound with specificity to the surface. After washing the plate to remove unbound reagents, a solution containing a second molecule that binds to the first ligand is added. This second molecule is linked to some kind of reporter system. The second molecule only binds to the plate if a PCR product has been produced whereby both oligonucleotide primers are incorporated into the final PCR products. The amount of the PCR product is then detected and quantified in a commercial plate reader much as ELISA reactions are detected and quantified. An ELISA-like system such as the one described here has been developed by the Raggio Italgene company under the C-Track trade name.

#### **5.3.7.2 VISUALIZATION OF AMPLIFICATION PRODUCTS**

Some of the quantitative measurement techniques described above may require visualization of amplification products. Amplification products are visualized, for example, in order to confirm amplification of the marker sequences. One typical visualization method involves staining of a gel with ethidium bromide and visualization under UV light. Alternatively, if the amplification products are integrally labeled with radio- or fluorometrically-labeled nucleotides, the amplification products may then be exposed to x-ray film or visualized under the appropriate stimulating spectra, following separation.

In one embodiment, visualization is achieved indirectly. Following separation of amplification products, a labeled, nucleic acid probe is brought into contact with the amplified marker sequence. The probe preferably is conjugated to a chromophore but may

be radiolabeled. In another embodiment, the probe is conjugated to a binding partner, such as an antibody or biotin, where the other member of the binding pair carries a detectable moiety.

5 In another embodiment, detection is by Southern blotting and hybridization with a labeled probe. The techniques involved in Southern blotting are well known to those of skill in the art and may be found in many standard books on molecular protocols. See Sambrook et al., 1989. Briefly, amplification products are separated by gel electrophoresis. The gel is then contacted with a membrane, such as nitrocellulose, permitting transfer of the nucleic acid and non-covalent binding. Subsequently, the  
10 membrane is incubated with a chromophore-conjugated probe that is capable of hybridizing with a target amplification product. Detection is by exposure of the membrane to x-ray film or ion-emitting detection devices.

One example of the foregoing is described in U.S. Pat. No. 5,279,721, incorporated by reference herein, which discloses an apparatus and method for the automated  
15 electrophoresis and transfer of nucleic acids. The apparatus permits electrophoresis and blotting without external manipulation of the gel and is ideally suited to carrying out methods according to the present invention.

#### **5.4 METHODS FOR MEASURING MOLECULAR MARKER DATA REFLECTIVE OF ABUNDANCE OF PROTEIN PRODUCTS OF 20 MOLECULAR MARKERS**

Measurement of the abundance of protein products of molecular markers in blood may be performed using a number of separation techniques combined with a monitoring system. For example, whole genome monitoring of protein (e.g., the “proteome,”) can be carried out using commercial systems such as a SELDI® Chip by Ciphergen. In addition,  
25 protein microarrays comprised of immobilized, preferably monoclonal, antibodies specific to a plurality of protein species encoded by the cell genome can be used. (e.g., The ProteinChip® Biomarker System, Ciphergen, Fremont, California). See also, for example, Lin, 2004, Modern Pathology, 1-9; Li, 2004, Journal of Urology 171, 1782-1787; Wadsworth, 2004, Clinical Cancer Research, 10, 1625-1632; Prieto, 2003, Journal of  
30 Liquid Chromatography & Related Technologies 26, 2315-2328; Coombes, 2003, Clinical Chemistry 49, 1615-1623; Mian, 2003, Proteomics 3, 1725-1737; Lehre *et al.*, 2003, BJU International 92, 223-225; and Diamond, 2003, Journal of the American Society for Mass Spectrometry 14, 760-765, which are hereby incorporated by reference in their entireties.

In one embodiment, antibodies can be used to measure protein products of the candidate molecular markers. Methods for making monoclonal antibodies are well known (see, *e.g.*, Harlow and Lane, 1988, *Antibodies: A Laboratory Manual*, Cold Spring Harbor, New York, which is incorporated in its entirety for all purposes). In one embodiment,  
5 monoclonal antibodies are raised against synthetic peptide fragments designed based on genomic sequence of the cell. With such an antibody array, proteins from the cell are contacted to the array and their binding is assayed with assays known in the art.

Immunoassays known to one of skill in the art can be used to detect and quantify protein levels. For example, ELISAs can be used to detect and quantify protein levels.  
10 ELISAs comprise preparing antigen, coating the well of a 96 well microtiter plate with the antigen, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase) to the well and incubating for a period of time, and detecting the presence of the antigen. In ELISAs the antibody of interest does not have to be conjugated to a detectable compound; instead, a  
15 second antibody (which recognizes the antibody of interest) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, a second antibody conjugated to a detectable compound may be added following the addition of the antigen of interest to the coated well. One of skill in the art would be knowledgeable as to the parameters that can  
20 be modified to increase the signal detected as well as other variations of ELISAs known in the art. In a preferred embodiment, an ELISA may be performed by coating a high binding 96-well microtiter plate (Costar) with 2µg/ml of rhu-IL-9 in PBS overnight. Following three washes with PBS, the plate is incubated with three-fold serial dilutions of Fab at 25°C for 1 hour. Following another three washes of PBS, 1µg/ml anti-human  
25 kappa-alkaline phosphatase-conjugate is added and the plate is incubated for 1 hour at 25°C. Following three washes with PBST, the alkaline phosphatase activity is determined in 50µl/AMP/PPMP substrate. The reactions are stopped and the absorbance at 560 nm is determined with a VMAX microplate reader. For further discussion regarding ELISAs see, *e.g.*, Ausubel et al, eds, 1994, *Current Protocols in Molecular Biology*, Vol. 1, John  
30 Wiley & Sons, Inc., New York at 11.2.1.

Protein levels may be determined by Western blot analysis. Further, protein levels as well as the phosphorylation of proteins can be determined by immunoprecipitation followed by Western blot analysis. Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X-

100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphatase and/or protease inhibitors (*e.g.*, EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (*e.g.*, 1 to 4 hours) at 40° C, adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 40° C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody of interest to immunoprecipitate a particular antigen can be assessed by, *e.g.*, western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (*e.g.*, pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.16.1.

Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (*e.g.*, 8%- 20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, incubating the membrane in blocking solution (*e.g.*, PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (*e.g.*, PBS-Tween 20), incubating the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, incubating the membrane with a secondary antibody (which recognizes the primary antibody, *e.g.*, an anti-human antibody) conjugated to an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase) or radioactive molecule (*e.g.*, <sup>32</sup>P or <sup>125</sup>I) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.8.1.

Protein expression levels can also be separated by two-dimensional gel electrophoresis systems. Two-dimensional gel electrophoresis is well-known in the art and typically involves isoelectric focusing along a first dimension followed by SDS-PAGE electrophoresis along a second dimension. See, *e.g.*, Hames *et al.*, 1990, *Gel Electrophoresis of Proteins: A Practical Approach*, IRL Press, New York; Shevchenko *et*

*al.*, 1996, *Proc. Natl. Acad. Sci. USA* 93:1440-1445; Sagliocco *et al.*, 1996, *Yeast* 12:1519-1533; Lander, 1996, *Science* 274:536-539. The resulting electropherograms can be analyzed by numerous techniques, including mass spectrometric techniques, Western blotting and immunoblot analysis using polyclonal and monoclonal antibodies, and  
5 internal and N-terminal micro-sequencing.

## 5.5 USES OF CLASSIFIERS IDENTIFIED

In exemplary embodiments, the classifiers constructed in accordance with the present invention can be used to detect, diagnose, prognose and/or monitor a trait in a test individual. In a specific embodiment, a classifier or classifier group constructed in  
10 accordance with Section 5.1 is used to detect, diagnose, prognose and/or monitor a disease in said test individual. In another embodiment, a classifier or classifier group constructed in accordance with Section 5.1 is used to detect, diagnose, prognose and/or monitor a reoccurrence of disease in said test individual. In another embodiment, a classifier or classifier group constructed in accordance with the invention is used to evaluate or predict  
15 the efficacy of treatment in a subject. In another embodiment, a classifier or classifier group constructed in accordance with the invention is used to predict whether a subject will be responsive to treatment and/or treatment outcomes. In another embodiment, a classifier or classifier group constructed in accordance with the invention is used to monitor and/or predict treatment compliance or non-compliance. In another embodiment,  
20 a classifier or classifier group constructed in accordance with the methods of the invention is indicative of the responsiveness of a subject to a stimulus (whether external or internal, e.g., smoke, pollution, sunlight, heat, and mutations) and is used to evaluate or predict the response of a subject to such stimulus.

In yet another embodiment, the molecular markers identified by the classifiers of  
25 the invention can be used independently of the classifier to detect, diagnose, prognose, predict and/or monitor a trait. In such embodiments, said detection, diagnosis, prognosis, prediction and/or monitoring of a test individual can be accomplished by monitoring the gene expression pattern or profile of the molecular markers identified by the classifier or classifier group of the invention of a test individual and comparing said pattern or profile  
30 to a gene expression pattern or profile of a control individual or group of individuals who have said trait. In another embodiment, the gene expression pattern or profile of the test individual can be compared with a control individual or group of individuals who do not have said trait. In another embodiment, the gene expression pattern or profile of the test individual is compared as between individuals or group of individuals who have said trait

and who do not have said trait. In yet another embodiment, the gene expression pattern or profile of the test individual is compared with the individuals used for the training population. In yet another embodiment, the gene expression pattern or profile of the test individual is compared with the individuals of the scoring population. As used herein, a  
5 “gene expression pattern” or “gene expression profile” indicates the combined pattern of the results of the analysis of the level of expression of two or more biomarkers of the invention including 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or all of the biomarkers of the classifier or classifier groups. A gene expression pattern or gene expression profile can result from the measurement of expression of the products of the biomarkers of the invention and can be  
10 done by measuring either the RNA or the proteins corresponding to said molecular marker using any any of the techniques described herein. For example techniques to measure expression of the RNA products of the biomarkers of the invention includes, PCR based methods (including RT-PCR and quantitative RT-PCR) and non PCR based method as well as microarray analysis. To measure protein products of the biomarkers of the  
15 invention, techniques include western blotting and ELISA analysis.

## 5.6 KITS

One embodiment of the present invention comprises kits for measuring molecular marker data by providing the materials necessary to measure the abundance of one or more of the products of one or more molecular markers of the classifier or classifier groups  
20 identified. Such kits may comprise materials and reagents required for measuring molecular marker data where the product of the molecular marker is RNA or protein. In some embodiments, such kits include microarrays wherein the microarray is comprised of oligonucleotides and/or DNA and/or RNA fragments which hybridize to one or more of the products of one or more of the molecular markers of a classifier or classifier group. In  
25 some embodiments, such kits may include primers for PCR of either the RNA product or the cDNA copy of the RNA product of the molecular marker or both. In some embodiments, such kits may include primers for PCR as well as probes for Quantitative PCR. In some embodiments, such kits may include multiple primers and multiple probes wherein some of said probes have different flourophores so as to permit multiplexing of  
30 multiple products of a single molecular marker or multiple products wherein each product results from a single molecular marker. In some embodiments, such kits may further include materials and reagents for creating cDNA from RNA. In some embodiments, such kits may include antibodies specific for the protein products of a molecular marker. Such kits may additionally comprise materials and reagents for isolating RNA and/or proteins

from a blood sample. Such kits may additionally comprise materials and reagents for isolating RNA and/or proteins from a non-blood tissue sample. In addition such kits may include materials and reagents for synthesizing cDNA from RNA isolated from a blood sample. In some embodiments of the present invention such kits may include, a computer  
5 program product embedded on computer readable media for determining whether a subject has a trait of interest. In some embodiments of the present invention, the kits of the invention may include a computer program product embedded on a computer readable media along with instructions.

In some embodiments, the invention provides kits for measuring the expression of  
10 one or more nucleic acid sequences of one or more molecular markers. In a specific embodiment, such kits measure the expression of one or more nucleic acid sequences associated with a molecular marker which has been determined according to the method of the invention as being indicative of a trait of interest. In accordance with this embodiment, the kits may comprise materials and reagents that are necessary for  
15 measuring the expression of particular nucleic acid sequence products of molecular markers identified by a classifier or classifier group of the invention. For example, a microarray or RT-PCR kit may be produced for a specific condition and contain only those reagents and materials necessary for measuring the levels of specific RNA transcript products of the molecular markers associated with the classifier or classifier groups  
20 selected in accordance with one embodiment of the invention. Alternatively, in some embodiments, the kits can comprise materials and reagents that are not limited to those required to measure the expression of particular nucleic acid sequences of any particular molecular marker. For example, in certain embodiments, the kits comprise materials and reagents necessary for measuring the levels of expression of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15,  
25 20, 25, 30, 35, 40, 45, 50 or more of the molecular markers of the invention, in addition to reagents and materials necessary for measuring the levels of the expression of at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50 or more genes other than the molecular markers of the invention. In other embodiments,  
30 the kits contain reagents and materials necessary for measuring the levels of expression of at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50 or more of the molecular markers of the invention, and 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 125, 150, 175, 200, 225, 250,

300, 350, 400, 450, or more genes that are not molecular markers of the invention, or 1-10, 1-100, 1-150, 1-200, 1-300, 1-400, 1-500, 1-1000, 25-100, 25-200, 25-300, 25-400, 25-500, 25-1000, 100-150, 100-200, 100-300, 100-400, 100-500, 100-1000 or 500-1000 genes that are not molecular markers of the invention.

5 For nucleic acid microarray kits, the kits generally comprise probes attached to a solid support surface. In one such embodiment, probes can be either oligonucleotides or longer length probes including probes ranging from 150 nucleotides in length to 800 nucleotides in length. The probes may be labeled with a detectable label. In a specific embodiment, the probes are specific for one or more of the products of a specific  
10 molecular marker identified following the methods of section 5.1. The microarray kits may comprise instructions for performing the assay and methods for interpreting and analyzing the data resulting from the performance of the assay. In a specific embodiment, the kits comprise instructions for diagnosing a trait of interest. The kits may also comprise hybridization reagents and/or reagents necessary for detecting a signal produced when a  
15 probe hybridizes to a target nucleic acid sequence. Generally, the materials and reagents for the microarray kits are in one or more containers. Each component of the kit is generally in its own a suitable container.

In certain embodiments, a nucleic acid microarray kit comprises materials and reagents necessary for measuring the levels of expression of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15,  
20 20, 25, 30, 35, 40, 45, 50 or more of the molecular markers of the invention, in addition to reagents and materials necessary for measuring the levels of the expression of at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50 or more genes other than the molecular markers of the invention. In other embodiments, a  
25 nucleic acid microarray kit contains reagents and materials necessary for measuring the levels of expression of at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50 or more of the molecular markers of the invention, and 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 125,  
30 150, 175, 200, 225, 250, 300, 350, 400, 450, or more genes that are not molecular markers of the invention, or 1-10, 1-100, 1-150, 1-200, 1-300, 1-400, 1-500, 1-1000, 25-100, 25-200, 25-300, 25-400, 25-500, 25-1000, 100-150, 100-200, 100-300, 100-400, 100-500, 100-1000 or 500-1000 genes that are not molecular markers of the invention.



For Quantitative PCR, the kits generally comprise pre-selected primers specific for particular nucleic acid sequences. The Quantitative PCR kits may also comprise enzymes suitable for amplifying nucleic acids (e.g., polymerases such as Taq), and deoxynucleotides and buffers needed for the reaction mixture for amplification. The Quantitative PCR kits may also comprise probes specific for the nucleic acid sequences associated with or indicative of a condition. The probes may or may not be labeled with a fluorophore. The probes may or may not be labeled with a quencher molecule. In some embodiments the Quantitative PCR kits also comprise components suitable for reverse-transcribing RNA including enzymes (e.g. reverse transcriptases such as AMV, MMLV and the like) and primers for reverse transcription along with deoxynucleotides and buffers needed for the reverse transcription reaction. Each component of the quantitative PCR kit is generally in its own suitable container. Thus, these kits generally comprise distinct containers suitable for each individual reagent, enzyme, primer and probe. Further, the quantitative PCR kits may comprise instructions for performing the assay and methods for interpreting and analyzing the data resulting from the performance of the assay. In a specific embodiment, the kits contain instructions for diagnosing a trait of interest.

For antibody based kits, the kit can comprise, for example: (1) a first antibody (which may or may not be attached to a solid support) which binds to a peptide, polypeptide or protein of interest; and, optionally, (2) a second, different antibody which binds to either the peptide, polypeptide or protein, or the first antibody and is conjugated to a detectable label (e.g., a fluorescent label, radioactive isotope or enzyme). In a specific embodiment, the peptide, polypeptide or protein of interest is associated with or indicative of a condition (e.g., a disease). The antibody-based kits may also comprise beads for conducting an immunoprecipitation. Each component of the antibody-based kits is generally in its own suitable container. Thus, these kits generally comprise distinct containers suitable for each antibody. Further, the antibody-based kits may comprise instructions for performing the assay and methods for interpreting and analyzing the data resulting from the performance of the assay. In a specific embodiment, the kits contain instructions for diagnosing a trait of interest.

## **5.7 EXEMPLARY NORMALIZATION ROUTINES**

A number of different normalization protocols can be used to normalize molecular marker data obtained using microarrays. Some such normalization protocols are described in this section. Typically, the normalization comprises normalizing the expression level measurement of each gene in a plurality of genes that is expressed by a subject. Many of

the normalization protocols described in this section are used to normalize microarray data. It will be appreciated that there are many other suitable normalization protocols that may be used in accordance with the present invention. All such protocols are within the scope of the present invention. Many of the normalization protocols found in this section are  
5 found in publicly available software, such as Microarray Explorer (Image Processing Section, Laboratory of Experimental and Computational Biology, National Cancer Institute, Frederick, MD 21702, USA).

One normalization protocol is Z-score of intensity. In this protocol, raw expression intensities are normalized by the (mean intensity)/(standard deviation) of raw intensities  
10 for all spots in a sample. For microarray data, the Z-score of intensity method normalizes each hybridized sample by the mean and standard deviation of the raw intensities for all of the spots in that sample. The mean intensity  $mnI_i$  and the standard deviation  $sdI_i$  are computed for the raw intensity of control genes. It is useful for standardizing the mean (to 0.0) and the range of data between hybridized samples to about -3.0 to +3.0. When using  
15 the Z-score, the Z differences ( $Z_{diff}$ ) are computed rather than ratios. The Z-score intensity ( $Z\text{-score}_{ij}$ ) for intensity  $I_{ij}$  for probe  $i$  (hybridization probe, protein, or other binding entity) and spot  $j$  is computed as:

$$Z\text{-score}_{ij} = (I_{ij} - mnI_i) / sdI_i,$$

and

$$20 \quad Z_{diff}(x,y) = Z\text{-score}_{xj} - Z\text{-score}_{yj}$$

where  $x$  represents the  $x$  channel and  $y$  represents the  $y$  channel.

Another normalization protocol is the median intensity normalization protocol in which the raw intensities for all spots in each sample are normalized by the median of the raw intensities. For microarray data, the median intensity normalization method  
25 normalizes each hybridized sample by the median of the raw intensities of control genes ( $medianI_i$ ) for all of the spots in that sample. Thus, upon normalization by the median intensity normalization method, the raw intensity  $I_{ij}$  for probe  $i$  and spot  $j$ , has the value  $Im_{ij}$  where,

$$30 \quad Im_{ij} = (I_{ij} / medianI_i).$$

Another normalization protocol is the log median intensity protocol. In this protocol, raw expression intensities are normalized by the log of the median scaled raw intensities of representative spots for all spots in the sample. For microarray data, the log

median intensity method normalizes each hybridized sample by the log of median scaled raw intensities of control genes ( $\text{median}I_i$ ) for all of the spots in that sample. As used herein, control genes are a set of genes that have reproducible accurately measured expression values. The value 1.0 is added to the intensity value to avoid taking the  
5  $\log(0.0)$  when intensity has zero value. Upon normalization by the median intensity normalization method, the raw intensity  $I_{ij}$  for probe  $i$  and spot  $j$ , has the value  $\text{Im}_{ij}$  where,  
$$\text{Im}_{ij} = \log(1.0 + (I_{ij} / \text{median}I_i)).$$

Yet another normalization protocol is the Z-score standard deviation log of  
10 intensity protocol. In this protocol, raw expression intensities are normalized by the mean log intensity ( $\text{mn}LI_i$ ) and standard deviation log intensity ( $\text{sd}LI_i$ ). For microarray data, the mean log intensity and the standard deviation log intensity is computed for the log of raw intensity of control genes. Then, the Z-score intensity  $Z\log S_{ij}$  for probe  $i$  and spot  $j$  is:

$$Z\log S_{ij} = (\log(I_{ij}) - \text{mn}LI_i) / \text{sd}LI_i.$$

15 Still another normalization protocol is the Z-score mean absolute deviation of log intensity protocol. In this protocol, raw expression intensities are normalized by the Z-score of the log intensity using the equation  $(\log(\text{intensity}) - \text{mean logarithm}) / \text{standard deviation logarithm}$ . For microarray data, the Z-score mean absolute deviation of log intensity protocol normalizes each bound sample by the mean and mean absolute deviation  
20 of the logs of the raw intensities for all of the spots in the sample. The mean log intensity  $\text{mn}LI_i$  and the mean absolute deviation log intensity  $\text{mad}LI_i$  are computed for the log of raw intensity of control genes. Then, the Z-score intensity  $Z\log A_{ij}$  for probe  $i$  and spot  $j$  is:

$$Z\log A_{ij} = (\log(I_{ij}) - \text{mn}LI_i) / \text{mad}LI_i.$$

Another normalization protocol is the user normalization gene set protocol. In this  
25 protocol, raw expression intensities are normalized by the sum of the genes in a user defined gene set in each sample. This method is useful if a subset of genes has been determined to have relatively constant expression across a set of samples. Yet another normalization protocol is the calibration DNA gene set protocol in which each sample is normalized by the sum of calibration DNA genes. As used herein, calibration DNA genes  
30 are genes that produce reproducible expression values that are accurately measured. Such genes tend to have the same expression values on each of several different microarrays. The algorithm is the same as user normalization gene set protocol described above, but the set is predefined as the genes flagged as calibration DNA.

Yet another normalization protocol is the ratio median intensity correction protocol. This protocol is useful in embodiments in which a two-color fluorescence labeling and detection scheme is used. In the case where the two fluors in a two-color fluorescence labeling and detection scheme are Cy3 and Cy5, measurements are  
5 normalized by multiplying the ratio (Cy3/Cy5) by medianCy5/medianCy3 intensities. If background correction is enabled, measurements are normalized by multiplying the ratio (Cy3/Cy5) by (medianCy5-medianBkgdCy5) / (medianCy3-medianBkgdCy3) where medianBkgd means median background levels.

10 In some embodiments, intensity background correction is used to normalize measurements. The background intensity data from a spot quantification programs may be used to correct spot intensity. Background may be specified as either a global value or on a per-spot basis. If the array images have low background, then intensity background correction may not be necessary.

## 5.8 EXEMPLARY DISEASES

15 As discussed *supra*, the present invention provides methods for developing classifiers that can be used to determine whether a patient has a certain trait including a disease. Exemplary diseases that can be identified include asthma, cancers, common late-onset Alzheimer's disease, diabetes, heart disease, hereditary early-onset Alzheimer's disease (George-Hyslop *et al.*, 1990, *Nature* 347: 194), hereditary nonpolyposis colon  
20 cancer, hypertension, infection, maturity-onset diabetes of the young (Barbosa *et al.*, 1976, *Diabete Metab.* 2: 160), mellitus, nonalcoholic fatty liver (NAFL) (Younossi, *et al.*, 2002, *Hepatology* 35, 746-752), nonalcoholic steatohepatitis (NASH) (James & Day, 1998, *J. Hepatol.* 29: 495-501), non-insulin-dependent diabetes mellitus, and polycystic kidney disease (Reeders *et al.*, 1987, *Human Genetics* 76: 348).

25 Disease also includes, blood disorder, blood lipid disease, autoimmune disease, arthritis (including osteoarthritis, rheumatoid arthritis, lupus, allergies, juvenile rheumatoid arthritis and the like), bone or joint disorder, a cardiovascular disorder (including heart failure, congenital heart disease; rheumatic fever, valvular heart disease; cor pulmonale, cardiomyopathy, myocarditis, pericardial disease; vascular diseases such as  
30 atherosclerosis, acute myocardial infarction, ischemic heart disease and the like), obesity, respiratory disease (including asthma, pneumonitis, pneumonia, pulmonary infections, lung disease, bronchiectasis, tuberculosis, cystic fibrosis, interstitial lung disease, chronic bronchitis emphysema, pulmonary hypertension, pulmonary thromboembolism, acute respiratory distress syndrome and the like), hyperlipidemias, endocrine disorder, immune

disorder, infectious disease, muscle wasting and whole body wasting disorder, neurological disorders (including migraines, seizures, epilepsy, cerebrovascular diseases, alzheimers, dementia, parkinsons, ataxic disorders, motor neuron diseases, cranial nerve disorders, spinal cord disorders, meningitis and the like) including neurodegenerative  
5 and/or neuropsychiatric diseases and mood disorders (including schizophrenia, anxiety, bipolar disorder; manic depression and the like, skin disorder, kidney disease, scleroderma, stroke, hereditary hemorrhage telangiectasia, diabetes, disorders associated with diabetes (e.g., PVD), hypertension, Gaucher's disease, cystic fibrosis, sickle cell anemia, liver disease, pancreatic disease, eye, ear, nose and/or throat disease, diseases affecting the  
10 reproductive organs, gastrointestinal diseases (including diseases of the colon, diseases of the spleen, appendix, gall bladder, and others) and the like. For further discussion of human diseases, see Mendelian Inheritance in Man: A Catalog of Human Genes and Genetic Disorders by Victor A. McKusick (12th Edition (3 volume set) June 1998, Johns Hopkins University Press, ISBN: 0801857422) and Harrison's Principles of Internal  
15 Medicine by Braunwald, Fauci, Kasper, Hauser, Longo, & Jameson (15th Edition 2001), the entirety of which is incorporated herein.

Cancers that can be identified using the inventive techniques of the present invention include, but are not limited to, human sarcomas and carcinomas, e.g., fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma,  
20 chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma,  
25 papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma,  
30 hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma; leukemias, e.g., acute lymphocytic leukemia and acute myelocytic leukemia (myeloblastic, promyelocytic, myelomonocytic, monocytic and erythroleukemia); chronic leukemia (chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia); and polycythemia vera, lymphoma (Hodgkin's disease

and non-Hodgkin's disease), multiple myeloma, Waldenström's macroglobulinemia, and heavy chain disease.

## 5.9 EXEMPLARY DATABASE ARCHITECTURES

In some embodiments, training population 44, candidate molecular marker data structure 58, patient database 68, and/or classifier database 70 comprise or are stored in one or more data warehouses. Data warehouses are typically structured as either relational databases or multidimensional data cubes. This section describes relational databases and multidimensional data cube architectures that can be used to store training data, candidate molecular marker lists, patient molecular marker data and/or classifiers of the present invention. More information on relational databases and multidimensional data cubes is found in Berson and Smith, 1997, *Data Warehousing, Data Mining and OLAP*, McGraw-Hill, New York; Freeze, 2000, *Unlocking OLAP with Microsoft SQL Server and Excel 2000*, IDG Books Worldwide, Inc., Foster City, California; and Thomson, 1997, *OLAP Solutions: Building Multidimensional Information Systems*, Wiley Computer Publishing, New York.

### 5.9.1 DATA ORGANIZATION

Databases have typically been used for operational purposes, such as order entry, accounting and inventory control. More recently, corporations and scientific projects have been building databases, called data warehouses or large on-line analytical processing (OLAP) databases, explicitly for the purposes of exploration and analysis. The "data warehouse" can be described as a subject-oriented, integrated, time-variant, nonvolatile collection of data in support of management decisions. Data warehouses are built using both relational databases and specialized multidimensional structures called data cubes. In some embodiments a database stored in computer 10 or stored in a computer addressable by computer 10 across wide area network 34 is a relational database or a datacube.

### 5.9.2 RELATIONAL DATABASES

Relational databases organize data into tables where each row corresponds to a basic entity or fact and each column represents a property of that entity. For example, a table can represent transactions in a bank, where each row corresponds to a single transaction, and each transaction has multiple attributes, such as the transaction amount, the account balance, the bank branch, and the customer. The relational table is referred to as a relation, a row as a tuple, and a column as an attribute or field. The attributes within a relation can be partitioned into two types: dimensions and measures. Dimensions and

measures are similar to independent and dependent variables in traditional analysis. For example, the bank branch and the customer would be dimensions, while the account balance would be a measure. A single relational database will often describe many heterogeneous but interrelated entities. For example, a database designed for a restaurant chain might maintain information about employees, products, and sales. The database schema defines the relations in a database, the relationships between those relations, and how the relations classify the entities of interest.

### 5.9.3 DATA CUBES

A data warehouse can be constructed as a relational database using either a star or snowflake schema and will provide a conceptual classifier of a multidimensional data set. Each axis in the corresponding data cube represents a dimension in a relational schema and consists of every possible value for that dimension. For example, an axis corresponding to states would have fifty values, one for each state. Each cell in the data cube corresponds to a unique combination of values for the dimensions. For instance, if there are two dimensions, "state" and "product", then there would be a cell for every unique combination of the two, e.g., one cell each for (California, Tea), (California, Coffee), (Florida, Tea), (Florida, Coffee), etc. Each cell contains one value per measure of the data cube. So if product production and consumption information is needed, then each cell would contain two values, one for the number of products of each type consumed in that state, and one for the number of products of each type produced in that state. Dimensions within a data warehouse are often augmented with a hierarchical structure. If each dimension has a hierarchical structure, then the data warehouse is not a single data cube but rather a lattice of data cubes.

### 5.10 EXEMPLARY PATIENT DATABASE

This section provides a more detailed description of a patient database 68 in accordance with one aspect of the invention. As described in Section 5.1, an exemplary patient database 68 includes a plurality of patient records 500 (Fig. 6). There is no limit on the number of patient records 500 that can be held in patient database 68. Database 68 can hold as few as one patient record 500. More typically, database 68 holds between 1 and 100 patient records, more than 100 patient records, more than a thousand patient records, more than ten thousand patient records, more than 100 thousand patient records, between 1 patient record and one million patient records, or more. Each patient record 500 preferably includes a patient identifier 502. As those skilled in database arts will appreciate, a patient

identifier 502 need not be explicitly enumerated in certain database systems. For instance, in some systems, a patient identifier 502 can simply be a patient record 500 identifier. However, in some embodiments, a patient identifier 502 can be a number that uniquely identifies a patient within a health care program or clinical trial.

5       An advantage of database 68 is that it has the capability of tracking molecular marker data profile 504 and trait characterization information 510 for each patient registered in database 68. In some embodiments, a molecular profile 504 is the abundance levels of a plurality of molecular marker products in blood specimens obtained from a patient in accordance with Section 5.2. In some embodiments, such abundance levels are  
10       normalized using any of the techniques disclosed in Section 5.7.

      In some embodiments, a molecular profile 504 comprises the processed microarray image data from the biological specimen obtained from the patient. In one example, molecular profile data 504 comprises molecular marker abundance information for all or a portion of the cellular constituents represented in a microarray, optional background signal  
15       information, and optional associated annotation information describing the probes used for the respective molecular marker. Molecular markers include, but are not limited to RNA (e.g., mRNA) and protein.

      In some embodiments, a molecular profile 504 represents the transcriptional state of cellular constituents in a biological specimen. However, in other embodiments, a  
20       molecular profile 504 can track aspects of the biological state other than or in addition to transcriptional state. Such other aspects of the biological state include, but are not limited to, the translational state, the activity state of cellular constituents in a biological sample. In some embodiments, for example, molecular profile 504 data is, in fact, protein levels for various proteins in the blood taken from the patient. Thus, in some embodiments,  
25       molecular profiles 504 comprise amounts or concentrations of the molecular markers in biological specimens obtained in accordance with Section 5.2.

      In one embodiment, the amount of at least one molecular marker that is tracked in a molecular profile 504 comprises abundances of at least one RNA species present in one or more cells in the blood obtained from the patient. Such abundances can be measured by a  
30       method comprising contacting a gene transcript array with RNA derived from one or more cells of the biological specimen, or with cDNA derived therefrom. A gene transcript array comprises a surface with attached nucleic acids or nucleic acid mimics. The nucleic acids or nucleic acid mimics are capable of hybridizing with the RNA species or with cDNA derived from the RNA species. In one particular embodiment, the abundance of the RNA



is measured by contacting a gene transcript array with the RNA from one or more cells of the biological specimen, or with nucleic acid derived from the RNA, such that the gene transcript array comprises a positionally addressable surface with attached nucleic acids or nucleic acid mimics, where the nucleic acids or nucleic acid mimics are capable of hybridizing with the RNA species, or with nucleic acid derived from the RNA species.

In some embodiments, a molecular profile 504 can include abundance information or activity information about ten or more molecular markers (e.g., genes or proteins), between ten and one thousand molecular markers, between one thousand and twenty thousand molecular markers, or more than twenty thousand molecular markers.

In some embodiments, in addition to or rather than providing abundance information or activity information for molecular markers, a molecular profile 504 tracks polymorphism information. Such polymorphism information includes, but is not limited to, single nucleotide polymorphisms (SNPs), SNP haplotypes, microsatellite markers, restriction fragment length polymorphisms (RFLPs), short tandem repeats, sequence length polymorphisms, DNA methylation, random amplified polymorphic DNA (RAPD), amplified fragment length polymorphisms (AFLP), and "simple sequence repeats." For more information on such polymorphisms, see generally, *The DNA Revolution* by Andrew H. Paterson 1996 (Chapter 2) in: *Genome Mapping in Plants* (ed. Andrew H. Paterson) by Academic Press/R. G. Landis Company, Austin, Tex., 7-21, which is hereby incorporated herein by reference in its entirety

SNPs occur approximately once every 600 base pairs in the genome. See, for example, Kruglyak and Nickerson, 2001, *Nature Genetics* 27, 235. Alleles making up blocks of such SNPs in close physical proximity are often correlated, resulting in reduced genetic variability and defining a limited number of "SNP haplotypes" each of which reflects descent from a single ancient ancestral chromosome. See Fullerton *et al.*, 2000, *Am. J. Hum. Genet.* 67, 881. Such haplotype structure is used in some embodiments of the present invention. Patil *et al.* found that a very dense set of SNPs is required to capture all the common haplotype information. See Patil *et al.*, 2001, *Science* 294, 1719-1723. DNA methylation is described in Grunau *et al.*, 2003, *Nucleic Acids Res.* 31, pp. 75-77.

RFLPs are the product of allelic differences between DNA restriction fragments caused by nucleotide sequence variability. As is well known to those of skill in the art, RFLPs are typically detected by extraction of genomic DNA and digestion with a restriction endonuclease. Generally, the resulting fragments are separated according to size and hybridized with a probe; single copy probes are preferred. As a result, restriction

fragments from homologous chromosomes are revealed. Differences in fragment size among alleles represent an RFLP (see, for example, Helentjaris *et al.*, 1985, Plant Mol. Bio. 5:109-118, and U.S. Pat. No. 5,324,631).

5 The phrase “random amplified polymorphic DNA” or “RAPD” refers to the amplification product of the distance between DNA sequences homologous to a single oligonucleotide primer appearing on different sites on opposite strands of DNA. Mutations or rearrangements at or between binding sites will result in polymorphisms as detected by the presence or absence of amplification product (see, for example, Welsh and McClelland, 1990, Nucleic Acids Res. 18:7213-7218; Hu and Quiros, 1991, Plant Cell  
10 Rep. 10:505-511). AFLP technology refers to a process that is designed to generate large numbers of randomly distributed molecular markers (see, for example, European Patent Application No. 0534858 A1).

“Simple sequence repeats” or “SSRs” are di-, tri- or tetra-nucleotide tandem repeats within a genome. The repeat region can vary in length between genotypes while  
15 the DNA flanking the repeat is conserved such that the same primers will work in a plurality of genotypes. A polymorphism between two genotypes represents repeats of different lengths between the two flanking conserved DNA sequences (see, for example, Akagi *et al.*, 1996, Theor. Appl. Genet. 93, 1071-1077; Bligh *et al.*, 1995, Euphytica 86:83-85; Struss *et al.*, 1998, Theor. Appl. Genet. 97, 308-315; Wu *et al.*, 1993, Mol. Gen.  
20 Genet. 241, 225-235; and U.S. Pat. No. 5,075,217). SSR are also known as satellites or microsatellites.

In addition to molecular profiles 50, patient records 500 include trait characterizations 510. In some embodiments, a trait characterization 510 comprises observations made by a patient’s physician. In some instances, the observations made by a  
25 physician include a code from the International Classification of Diseases, 9<sup>th</sup> Revision, prepared by the Department of Health and Human Services (ICD-9 codes), or an equivalent, and dates such observations were made.

## **5.11 EXEMPLARY GENES AS CANDIDATE MOLECULAR MARKERS**

Non-limiting examples of genes useful as molecular markers for use in the  
30 invention can include, but are not limited to, genes specific for or involved in a particular biological process, such as apoptosis, differentiation, stress response, aging, proliferation, etc.; cellular mechanism genes, e.g., cell-cycle, signal transduction, metabolism of toxic compounds, and the like; disease associated genes, e.g., genes involved in cancer, schizophrenia, diabetes, high blood pressure, atherosclerosis, viral-host interaction and

infection and the like. Exemplary genes can also include immune responsive genes. Further examples of genes can include, but are not limited to, oncogenes whose expression within a cell induces that cell to become converted from a normal cell into a tumor cell. See for example Hanahan & Weinberg, 2000, *Cell* 100:57; Yokota., 2000, *Carcinogenesis* 21:497. Further examples of genes can include, but are not limited to cytokine genes. See, for example, Rubinstein *et al.*, 1998, *Cytokine Growth Factor Rev.* 9:175-81. Other examples of genes can include idiotype protein genes (*e.g.*, Benezra., *et al.*, 2001 *Oncogene* 20:8334-41; Norton, 2000, *J. Cell Sci.* 113:3897), prion genes (*e.g.*, Prusiner *et al.*, 1998, *Cell* 93:337-48; Safar & Prusiner, 1998, *Prog. Brain Res.* 117:421); genes that express molecules that induce angiogenesis (*e.g.*, Gould & Wagner, 2002, *Hum. Pathol.* 33:1061); genes encoding adhesion molecules (*e.g.*, Chothia, & Jones, 1997, *Annu. Rev. Biochem.* 66:823; Parise *et al.*, 2000, *Semin. Cancer Biol.* 10:407-14); genes encoding cell surface receptors (*e.g.*, Deller and Jones, 2000, *Curr. Opin. Struct. Biol.* 10:213); genes of proteins that are involved in metastasizing and/or invasive processes (*e.g.*, Boyd, 1996, *Cancer Metastasis Rev.* 15:77; Yokota, 2000, *Carcinogenesis* 21:497); genes of proteases as well as of molecules that regulate apoptosis and the cell cycle (*e.g.*, Matrisian, 1999, *Curr. Biol.* 9:R776; Krepela, 2001, *Neoplasia* 48:332; Basbaum and Werb, 1996, *Curr. Opin. Cell Biol.* 8:731; Birkedal-Hansen *et al.*, 1993, *Crit. Rev. Oral Biol. Med.* 4:197-250; Mignatti and Rifkin, 1993, *Physiol. Rev.* 73:161; Stetler-Stevenson *et al.*, 1993, *Annu. Rev. Cell Biol.* 9:541; Brinkerhoff and Matrisan, 2002, *Nature Reviews* 3:207; Strasser. *et al.*, 2000, *Annu. Rev. Biochem.* 69:217; Chao and Korsmeyer, 1998, *Annu. Rev. Immunol.* 16:395; Mullauer *et al.*, 2001, *Mutat. Res.* 488:211; Fotadar *et al.*, 1996, *Prog. Cell Cycle Res.* 2:147; Reed., 2000, *Am. J. Pathol.* 157:1415; D'Ari, 2001, *Bioassays* 23:563); or multi-drug resistance genes, such as the MDR1 gene. In one embodiment, a gene is an immune response gene or a non-immune response gene such as cytokines (*e.g.*, interleukins and interferons such as TNF-alpha, IL-10, IL-12, IL-2, IL-4, IL-10, IL-12, IL-13, TGF-Beta, IFN-gamma; immunoglobulins, complement and the like). See, for example, Bellardelli, 1995, *Role of interferons and other cytokines in the regulation of the immune response* *APMIS* 103: 161.

## 5.12 CLUSTERING TECHNIQUES

In some embodiments, clustering is used. For instance, clustering can be used in step 204 to visualize the relationship between the data measured for a plurality of molecular markers in step 202. In some embodiments, any of the clustering techniques described in Draghici, *Data Analysis Tools For DNA Microarrays*, 2003, Chapman &

Hall, CRC Press, New York, pp. 263-297, which is hereby incorporated by reference in its entirety, are used in the present invention. Clustering is also described on pages 211-256 of Duda and Hart, *Pattern Classification and Scene Analysis*, 1973, John Wiley & Sons, Inc., New York, which is hereby incorporated by reference. As described in Section 6.7 of Duda, the clustering problem is described as one of finding natural groupings in a dataset. To identify natural groupings, two issues are addressed. First, a way to measure similarity (or dissimilarity) between two samples is determined. This metric (similarity measure) is used to ensure that the samples in one cluster are more like one another than they are to samples in other clusters. Second, a mechanism for partitioning the data into clusters using the similarity measure is determined.

Similarity measures are discussed in Section 6.7 of Duda, where it is stated that one way to begin a clustering investigation is to define a distance function and to compute the matrix of distances between all pairs of samples in a dataset. If distance is a good measure of similarity, then the distance between samples in the same cluster will be significantly less than the distance between samples in different clusters. However, as stated on page 215 of Duda, clustering does not require the use of a distance metric. For example, a nonmetric similarity function  $s(x, x')$  can be used to compare two vectors  $x$  and  $x'$ . Conventionally,  $s(x, x')$  is a symmetric function whose value is large when  $x$  and  $x'$  are somehow "similar". An example of a nonmetric similarity function  $s(x, x')$  is provided on page 216 of Duda.

Once a method for measuring "similarity" or "disimilarity" between points in a dataset has been selected, clustering requires a criterion function that measures the clustering quality of any partition of the data. Partitions of the data set that extremize the criterion function are used to cluster the data. See page 217 of Duda. Criterion functions are discussed in Section 6.8 of Duda.

More recently, Duda et al., *Pattern Classification*, 2<sup>nd</sup> edition, John Wiley & Sons, Inc. New York, has been published. Pages 537-563 describe clustering in detail. More information on clustering techniques can be found in Kaufman and Rousseeuw, 1990, *Finding Groups in Data: An Introduction to Cluster Analysis*, Wiley, New York, NY; Everitt, 1993, *Cluster analysis* (3d ed.), Wiley, New York, NY; and Backer, 1995, *Computer-Assisted Reasoning in Cluster Analysis*, Prentice Hall, Upper Saddle River, New Jersey. Now that an overview of clustering techniques has been given, more specific examples of clustering that can be performed in the methods described in Section 5.1 is presented.

### 5.12.1 HIERARCHICAL CLUSTERING TECHNIQUES

Hierarchical cluster analysis is a statistical method for finding relatively homogenous clusters of elements based on measured data. Consider a sequence of partitions of  $n$  samples into  $c$  clusters. The first of these is a partition into  $n$  clusters, each cluster containing exactly one sample. The next is a partition into  $n-1$  clusters, the next is partition into  $n-2$ , and so on until the  $n^{\text{th}}$ , in which all the samples form one cluster. Level  $k$  in the sequence of partitions occurs when  $c = n - k + 1$ . Thus, level one corresponds to  $n$  clusters and level  $n$  corresponds to one cluster. Given any two samples  $x$  and  $x^*$ , at some level they will be grouped together in the same cluster. If the sequence has the property that whenever two samples are in the same cluster at level  $k$  they remain together at all higher levels, then the sequence is said to be a hierarchical clustering. Duda et al., 2001, Pattern Classification, 2<sup>nd</sup> edition, John Wiley & Sons, New York, 2001: 551. Examples of hierarchical clustering includes agglomerative clustering using nearest-neighbor algorithm, farthest-neighbor algorithm, the average linkage algorithm, the centroid algorithm, or the sum-of-squares algorithm. See, for example WO03100557.

#### 5.12.1.1 CLUSTERING WITH PEARSON CORRELATION COEFFICIENTS

In some embodiments of the present invention, molecular marker data data is clustered using agglomerative hierarchical clustering with Pearson correlation coefficients. In this form of clustering, similarity is determined using Pearson correlation coefficients between sets of molecular marker data measurements. Other metrics that can be used, in addition to the Pearson correlation coefficient, include but are not limited to, a Euclidean distance, a squared Euclidean distance, a Euclidean sum of squares, a Manhattan metric, and a squared Pearson correlation coefficient. Such metrics can be computed using SAS (Statistics Analysis Systems Institute, Cary, North Carolina) or S-Plus (Statistical Sciences, Inc., Seattle, Washington).

#### 5.12.1.2 DIVISIVE CLUSTERING

In some embodiments, the hierarchical clustering technique used to cluster molecular marker data measurements is a divisive clustering procedure. Divisive (top-down clustering) procedures start with all of the samples in one cluster and form the sequence by successfully splitting clusters. Divisive clustering techniques are classified as either a polythetic or a monothetic method. A polythetic approach divides clusters into arbitrary subsets.

### 5.12.2 K-MEANS CLUSTERING

In k-means clustering, sets of molecular marker data measurements are randomly assigned to K user specified clusters. The centroid of each cluster is computed by averaging the value of the vectors in each cluster. Then, for each  $i = 1, \dots, N$ , the distance  
5 between vector  $x_i$  and each of the cluster centroids is computed. Each vector  $x_i$  is then reassigned to the cluster with the closest centroid. Next, the centroid of each affected cluster is recalculated. The process iterates until no more reassignments are made. See, for example, Duda *et al.*, 2001, *Pattern Classification*, John Wiley & Sons, New York, NY, pp. 526-528. A related approach is the fuzzy k-means clustering algorithm, which is  
10 also known as the fuzzy c-means algorithm. In the fuzzy k-means clustering algorithm, the assumption that every set of molecular marker data measurements is in exactly one cluster at any given time is relaxed so that every set has some graded or "fuzzy" membership in a cluster. See Duda *et al.*, 2001, *Pattern Classification*, John Wiley & Sons, New York, NY, pp. 528-530.

### 15 5.12.3 JARVIS-PATRICK CLUSTERING

Jarvis-Patrick clustering is a nearest-neighbor non-hierarchical clustering method in which a set of objects is partitioned into clusters on the basis of the number of shared nearest-neighbors. In the standard implementation advocated by Jarvis and Patrick, 1973, *IEEE Trans. Comput.*, C-22:1025-1034, a preprocessing stage identifies the K  
20 nearest-neighbors of each object in the dataset. In the subsequent clustering stage, two objects  $i$  and  $j$  join the same cluster if (i)  $i$  is one of the K nearest-neighbors of  $j$ , (ii)  $j$  is one of the K nearest-neighbors of  $i$ , and (iii)  $i$  and  $j$  have at least  $k_{\min}$  of their K nearest-neighbors in common, where K and  $k_{\min}$  are user-defined parameters. The method has been widely applied to clustering chemical structures on the basis of fragment  
25 descriptors and has the advantage of being much less computationally demanding than hierarchical methods, and thus more suitable for large databases. Jarvis-Patrick clustering can be performed using the Jarvis-Patrick Clustering Package 3.0 (Barnard Chemical Information, Ltd., Sheffield, United Kingdom).

### 5.13 MOLECULAR MARKERS

30 Molecular marker is used herein to mean a gene or genetic element. All genes and genetic elements are considered molecular markers, but the invention teaches how to identify molecular markers useful for diagnosing a trait of interest.

## 5.14 REPRESENTATIVE MATHEMATICAL MODELS THAT CAN BE USED TO BUILD CLASSIFIERS

This section describes various mathematical models that can be used to build classifier in accordance with the methods of the present invention.

5

### 5.14.1 REGRESSION CLASSIFIERS

In some embodiments, the classifier constructed in step 216 is a regression classifier, preferably a logistic regression classifier. Such a regression classifier includes a coefficient for each of the molecular markers selected in the last instance of step 214. In  
10 such embodiments, the coefficients for the regression classifier are computed using, for example, a maximum likelihood approach. In such a computation, the data measured for the molecular markers in step 206 (*e.g.*, RT-PCR data) is used. In particular embodiments, molecular marker data from only two trait subgroups is used and the dependent variable is absence or presence of a particular trait in the subjects for which molecular marker data is  
15 available. As in the case of step 210, the two different trait subgroups can, for example, respectively represent a diseased and nondiseased state, a first diseased state (*e.g.* liver cancer) and a second phenotypically similar (*e.g.* hepatitis B) or unrelated diseased state (*e.g.*, Alzheimer's disease), those subjects that are responsive to drug therapy and those subjects that are not responsive to drug therapy, or subjects that have been subjected to a  
20 perturbation (*e.g.*, drug treatment) versus those subjects that have not been subjected to a perturbation.

In another specific embodiment, training population 44 consists of a plurality of trait subgroups (*e.g.*, three or more trait subgroups, four or more specific trait subgroups, *etc.*). In this specific embodiment, a generalization of the logistic regression model that  
25 handles multicategory responses can be used in step 216 to develop a classifier that discriminates between the various trait subgroups found in the training population. For example, measured data for selected molecular markers can be applied to any of the multicategory logit models described in Agresti, *An Introduction to Categorical Data Analysis*, 1996, John Wiley & Sons, Inc., New York, Chapter 8, which is hereby  
30 incorporated herein by reference in its entirety, in order to develop a classifier capable of discriminating between any of a plurality of trait subgroups represented in a training population.

### 5.14.2 NEURAL NETWORKS

The present invention is not limited to the use of logistic regression. In some embodiments, the data measured for the molecular markers in step 206 (e.g., RT-PCR data) can be used to train a neural network.

5 In some embodiments, a neural network is derived in each successive instance of step 216 of Fig. 2A using the combination of molecular markers selected in the corresponding instance of step 214 of Fig. 2A. A neural network is a two-stage regression or classification classifier. A neural network has a layered structure that includes a layer of input units (and the bias) connected by a layer of weights to a layer of output units. For  
10 regression, the layer of output units typically includes just one output unit. However, neural networks can handle multiple quantitative responses in a seamless fashion.

In multilayer neural networks, there are input units (input layer), hidden units (hidden layer), and output units (output layer). There is, furthermore, a single bias unit that is connected to each unit other than the input units. Neural networks are described in  
15 Duda *et al.*, 2001, *Pattern Classification*, Second Edition, John Wiley & Sons, Inc., New York; and Hastie *et al.*, 2001, *The Elements of Statistical Learning*, Springer-Verlag, New York.

The basic approach to the use of neural networks is to start with an untrained network, present a training pattern to the input layer, and to pass signals through the net  
20 and determine the output at the output layer. These outputs are then compared to the target values; any difference corresponds to an error. This error or criterion function is some scalar function of the weights and is minimized when the network outputs match the desired outputs. Thus, the weights are adjusted to reduce this measure of error. For regression, this error can be sum-of-squared errors. For classification, this error can be  
25 either squared error or cross-entropy (deviation). See, e.g., Hastie *et al.*, 2001, *The Elements of Statistical Learning*, Springer-Verlag, New York.

Three commonly used training protocols are stochastic, batch, and on-line. In stochastic training, patterns are chosen randomly from the training set and the network weights are updated for each pattern presentation. Multilayer nonlinear networks trained  
30 by gradient descent methods such as stochastic back-propagation perform a maximum-likelihood estimation of the weight values in the classifier defined by the network topology. In batch training, all patterns are presented to the network before learning takes place. Typically, in batch training, several passes are made through the training data. In online training, each pattern is presented once and only once to the net.



In some embodiments, consideration is given to starting values for weights. If the weights are near zero, then the operative part of the sigmoid commonly used in the hidden layer of a neural network (see, e.g., Hastie *et al.*, 2001, *The Elements of Statistical Learning*, Springer-Verlag, New York) is roughly linear, and hence the neural network collapses into an approximately linear classifier. In some embodiments, starting values for weights are chosen to be random values near zero. Hence the classifier starts out nearly linear, and becomes nonlinear as the weights increase. Individual units localize to directions and introduce nonlinearities where needed. Use of exact zero weights leads to zero derivatives and perfect symmetry, and the algorithm never moves. Alternatively, starting with large weights often leads to poor solutions.

Since the scaling of inputs determines the effective scaling of weights in the bottom layer, it can have a large effect on the quality of the final solution. Thus, in some embodiments, at the outset all expression values are standardized to have mean zero and a standard deviation of one. This ensures all inputs are treated equally in the regularization process, and allows one to choose a meaningful range for the random starting weights. With standardization inputs, it is typical to take random uniform weights over the range  $[-0.7, +0.7]$ .

A recurrent problem in the use of three-layer networks is the optimal number of hidden units to use in the network. The number of inputs and outputs of a three-layer network are determined by the problem to be solved. In embodiments of the present invention, the number of inputs for a given neural network can, in some embodiments, equal the number of molecular markers selected in the corresponding instance of step 214. In other embodiments, for each input, two or more molecular markers will be selected (for example wherein ratios of genes (A/B) are utilized. The number of outputs for the neural network will typically be just one (ie wherein the output neuron is one dimensional e.g. health vs. disease). If there are additional input dimensions, new additional output neurons may be created. In some embodiments more than one output is used so that more than just two states can be defined by the network. If too many hidden units are used in a neural network, the network will have too many degrees of freedom and is trained too long, there is a danger that the network will overfit the data. If there are too few hidden units, the training set cannot be learned. Generally speaking, however, it is better to have too many hidden units than too few. With too few hidden units, the classifier might not have enough flexibility to capture the nonlinearities in the data; with too many hidden units, the extra weight can be shrunk towards zero if appropriate regularization or pruning, as described

below, is used. In typical embodiments, the number of hidden units is somewhere in the range of 5 to 100, with the number increasing with the number of inputs and number of training cases.

One general approach to determining the number of hidden units to use is to apply a regularization approach. In the regularization approach, a new criterion function is constructed that depends not only on the classical training error, but also on classifier complexity. Specifically, the new criterion function penalizes highly complex classifiers; searching for the minimum in this criterion is to balance error on the training set with error on the training set plus a regularization term, which expresses constraints or desirable properties of solutions:

$$J = J_{\text{pat}} + \lambda J_{\text{reg}}.$$

The parameter  $\lambda$  is adjusted to impose the regularization more or less strongly. In other words, larger values for  $\lambda$  will tend to shrink weights towards zero: typically cross-validation with a validation set is used to estimate  $\lambda$ . This validation set can be obtained by setting aside a random subset of the population measured in step 202 of Fig. 2A. Other forms of penalty have been proposed, for example the weight elimination penalty (see, e.g., Hastie *et al.*, 2001, *The Elements of Statistical Learning*, Springer-Verlag, New York).

Another approach to determine the number of hidden units to use is to eliminate - prune - weights that are least needed. In one approach, the weights with the smallest magnitude are eliminated (set to zero). Such magnitude-based pruning can work, but is nonoptimal; sometimes weights with small magnitudes are important for learning and training data. In some embodiments, rather than using a magnitude-based pruning approach, Wald statistics are computed. The fundamental idea in Wald Statistics is that they can be used to estimate the importance of a hidden unit (weight) in a classifier. Then, hidden units having the least importance are eliminated (by setting their input and output weights to zero). Two algorithms in this regard are the *Optimal Brain Damage* (OBD) and the *Optimal Brain Surgeon* (OBS) algorithms that use second-order approximation to predict how the training error depends upon a weight, and eliminate the weight that leads to the smallest increase in training error.

Optimal Brain Damage and Optimal Brain Surgeon share the same basic approach of training a network to local minimum error at weight  $w$ , and then pruning a weight that leads to the smallest increase in the training error. The predicted functional increase in the error for a change in full weight vector  $\delta w$  is:

$$\delta J = \left( \frac{\partial J}{\partial \mathbf{w}} \right)' \cdot \delta \mathbf{w} + \frac{1}{2} \delta \mathbf{w}' \cdot \frac{\partial^2 J}{\partial \mathbf{w}^2} \cdot \delta \mathbf{w} + O(\|\delta \mathbf{w}\|^3)$$

where  $\frac{\partial^2 J}{\partial \mathbf{w}^2}$  is the Hessian matrix. The first term vanishes because we are at a local minimum in error; third and higher order terms are ignored. The general solution for minimizing this function given the constraint of deleting one weight is:

$$\delta \mathbf{w} = - \frac{w_q}{[\mathbf{H}^{-1}]_{qq}} \mathbf{H}^{-1} \cdot \mathbf{u}_q \quad \text{and} \quad L_q = \frac{1}{2} - \frac{w_q^2}{[\mathbf{H}^{-1}]_{qq}}$$

Here,  $\mathbf{u}_q$  is the unit vector along the  $q$ th direction in weight space and  $L_q$  is approximation to the saliency of the weight  $q$  - the increase in training error if weight  $q$  is pruned and the other weights updated  $\delta \mathbf{w}$ . These equations require the inverse of  $\mathbf{H}$ . One method to calculate this inverse matrix is to start with a small value,  $H_0^{-1} = \alpha^{-1} \mathbf{I}$ , where  $\alpha$  is a small parameter - effectively a weight constant. Next the matrix is updated with each pattern according to

$$\mathbf{H}_{m+1}^{-1} = \mathbf{H}_m^{-1} - \frac{\mathbf{H}_m^{-1} \mathbf{X}_{m+1} \mathbf{X}_{m+1}^T \mathbf{H}_m^{-1}}{\frac{n}{a_m} + \mathbf{X}_{m+1}^T \mathbf{H}_m^{-1} \mathbf{X}_{m+1}} \quad \text{Eqn. 1}$$

where the subscripts correspond to the pattern being presented and  $a_m$  decreases with  $m$ . After the full training set has been presented, the inverse Hessian matrix is given by  $\mathbf{H}^{-1} = H_n^{-1}$ . In algorithmic form, the Optimal Brain Surgeon method is:

begin initialize  $n_H, \mathbf{w}, \theta$   
train a reasonably large network to minimum error  
do compute  $\mathbf{H}^{-1}$  by Eqn. 1

$$q^* \leftarrow \arg \min_q w_q^2 / (2[\mathbf{H}^{-1}]_{qq}) \quad (\text{saliency } L_q)$$

$$\mathbf{w} \leftarrow \mathbf{w} - \frac{w_{q^*}}{[\mathbf{H}^{-1}]_{q^*q^*}} \mathbf{H}^{-1} \mathbf{e}_{q^*} \quad (\text{saliency } L_q)$$

until  $J(\mathbf{w}) > \theta$   
return  $\mathbf{w}$   
end

The Optimal Brain Damage method is computationally simpler because the calculation of the inverse Hessian matrix in line 3 is particularly simple for a diagonal matrix. The above algorithm terminates when the error is greater than a criterion initialized to be  $\theta$ . Another approach is to change line 6 to terminate when the change in  $J(\mathbf{w})$  due to elimination of a weight is greater than some criterion value.

In some embodiments, the back-propagation neural network (see, for example Abdi, 1994, "A neural network primer", J. Biol System. 2, 247-283) containing a single hidden layer of ten neurons (ten hidden units) found in EasyNN-Plus version 4.0g software package (Neural Planner Software Inc.) is used. In one specific example, parameter values within the EasyNN-Plus program were set as follows: learning parameter = 0.6, and momentum parameter = 0.8. In some embodiments in which the EasyNN-Plus version 4.0g software package is used, "outlier" samples are identified by performing twenty independently-seeded trials involving 20,000 learning cycles each.

### 5.14.3 CLUSTERING

In some embodiments, the expression values for select genes are used to cluster a training set. For example, consider the case in which ten genes are used. Each member  $\mathbf{m}$  of the training population will have expression values for each of the ten genes. Such values from a member  $\mathbf{m}$  in the training population define the vector:

$X_{1\mathbf{m}}$	$X_{2\mathbf{m}}$	$X_{3\mathbf{m}}$	$X_{4\mathbf{m}}$	$X_{5\mathbf{m}}$	$X_{6\mathbf{m}}$	$X_{7\mathbf{m}}$	$X_{8\mathbf{m}}$	$X_{9\mathbf{m}}$	$X_{10\mathbf{m}}$
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where  $X_{i\mathbf{m}}$  is the expression level of the  $i^{\text{th}}$  gene in organism  $\mathbf{m}$ . If there are  $\mathbf{m}$  organisms in the training set, selection of  $i$  genes will define  $\mathbf{m}$  vectors. Note that the methods of the present invention do not require that each expression value of every single gene used in the vectors be represented in every single vector  $\mathbf{m}$ . In other words, data from a subject in which one of the  $i^{\text{th}}$  genes is not found can still be used for clustering. In such instances, the missing expression value is assigned either a "zero" or some other normalized value. In some embodiments, prior to clustering, the gene expression values are normalized to have a mean value of zero and unit variance.

Those members of the training population that exhibit similar expression patterns across the training group will tend to cluster together. A particular combination of genes of the present invention is considered to be a good classifier in this aspect of the invention when the vectors cluster into the trait groups found in the training population. For instance, if the training population includes patients with no osteoarthritis, mild

osteoarthritis, moderate osteoarthritis, marked osteoarthritis, and severe osteoarthritis an ideal clustering classifier will cluster the population into five groups, with each group uniquely representing either absence or one of the four stages of osteoarthritis. In some embodiments, the clustering classifier simply clusters the population into a first subgroup (a first cluster) that does not have osteoarthritis and a second subgroup (a second cluster) that has osteoarthritis. In some embodiments, the classifier clusters the data into a first subgroup that has a particular stage of osteoarthritis (*e.g.*, mild) and two or more subgroups that do not include subjects having the particular stage of osteoarthritis represented in the first subgroup.

Clustering is described on pages 211-256 of Duda and Hart, *Pattern Classification and Scene Analysis*, 1973, John Wiley & Sons, Inc., New York. As described in Section 6.7 of Duda, the clustering problem is described as one of finding natural groupings in a dataset. To identify natural groupings, two issues are addressed. First, a way to measure similarity (or dissimilarity) between two samples is determined. This metric (similarity measure) is used to ensure that the samples in one cluster are more like one another than they are to samples in other clusters. Second, a mechanism for partitioning the data into clusters using the similarity measure is determined.

Similarity measures are discussed in Section 6.7 of Duda, where it is stated that one way to begin a clustering investigation is to define a distance function and to compute the matrix of distances between all pairs of samples in a dataset. If distance is a good measure of similarity, then the distance between samples in the same cluster will be significantly less than the distance between samples in different clusters. However, as stated on page 215 of Duda, clustering does not require the use of a distance metric. For example, a nonmetric similarity function  $s(x, x')$  can be used to compare two vectors  $x$  and  $x'$ . Conventionally,  $s(x, x')$  is a symmetric function whose value is large when  $x$  and  $x'$  are somehow “similar”. An example of a nonmetric similarity function  $s(x, x')$  is provided on page 216 of Duda.

Once a method for measuring “similarity” or “dissimilarity” between points in a dataset has been selected, clustering requires a criterion function that measures the clustering quality of any partition of the data. Partitions of the data set that extremize the criterion function are used to cluster the data. See page 217 of Duda. Criterion functions are discussed in Section 6.8 of Duda.

More recently, Duda *et al.*, *Pattern Classification*, 2<sup>nd</sup> edition, John Wiley & Sons, Inc. New York, has been published. Pages 537-563 describe clustering in detail. More

information on clustering techniques can be found in Kaufman and Rousseeuw, 1990, *Finding Groups in Data: An Introduction to Cluster Analysis*, Wiley, New York, NY; Everitt, 1993, *Cluster analysis* (3d ed.), Wiley, New York, NY; and Backer, 1995, *Computer-Assisted Reasoning in Cluster Analysis*, Prentice Hall, Upper Saddle River, New Jersey. Particular exemplary clustering techniques that can be used in the present invention include, but are not limited to, hierarchical clustering (agglomerative clustering using nearest-neighbor algorithm, farthest-neighbor algorithm, the average linkage algorithm, the centroid algorithm, or the sum-of-squares algorithm), k-means clustering, fuzzy k-means clustering algorithm, and Jarvis-Patrick clustering.

#### 5.14.4 PRINCIPAL COMPONENT ANALYSIS

Principal component analysis (PCA) has been proposed to analyze gene expression data. Principal component analysis is a classical technique to reduce the dimensionality of a data set by transforming the data to a new set of variable (principal components) that summarize the features of the data. See, for example, Jolliffe, 1986, *Principal Component Analysis*, Springer, New York. Principal components (PCs) are uncorrelated and are ordered such that the  $k^{\text{th}}$  PC has the  $k^{\text{th}}$  largest variance among PCs. The  $k^{\text{th}}$  PC can be interpreted as the direction that maximizes the variation of the projections of the data points such that it is orthogonal to the first  $k - 1$  PCs. The first few PCs capture most of the variation in the data set. In contrast, the last few PCs are often assumed to capture only the residual 'noise' in the data.

PCA can also be used to create a classifier in accordance with the present invention. In such an approach, vectors for the select genes described in the present invention can be constructed in the same manner described for clustering above. In fact, the set of vectors, where each vector represents the expression values for the select genes from a particular member of the training population, can be considered a matrix. In some embodiments, this matrix is represented in a Free-Wilson method of qualitative binary description of monomers (Kubinyi, 1990, *3D QSAR in drug design theory methods and applications*, Pergamon Press, Oxford, pp 589-638), and distributed in a maximally compressed space using PCA so that the first principal component (PC) captures the largest amount of variance information possible, the second principal component (PC) captures the second largest amount of all variance information, and so forth until all variance information in the matrix has been accounted for.

Then, each of the vectors (where each vector represents a member of the training population) is plotted. Many different types of plots are possible. In some embodiments, a

one-dimensional plot is made. In this one-dimensional plot, the value for the first principal component from each of the members of the training population is plotted. In this form of plot, the expectation is that members of a first subgroup (e.g. those subjects that do not have osteoarthritis) will cluster in one range of first principal component values and  
5 members of a second subgroup (e.g., those subjects that have osteoarthritis) will cluster in a second range of first principal component values.

In one ideal example, the training population comprises two subgroups: “control” and “patients with osteoarthritis.” The first principal component is computed using the molecular marker expression values for the select genes of the present invention across the  
10 entire training population data set. Then, each member of the training set is plotted as a function of the value for the first principal component. In this ideal example, those members of the training population in which the first principal component is positive are the “responders” and those members of the training population in which the first principal component is negative are “patients with osteoarthritis.”

15 In some embodiments, the members of the training population are plotted against more than one principal component. For example, in some embodiments, the members of the training population are plotted on a two-dimensional plot in which the first dimension is the first principal component and the second dimension is the second principal component. In such a two-dimensional plot, the expectation is that members of each  
20 subgroup represented in the training population will cluster into discrete groups. For example, a first cluster of members in the two-dimensional plot will represent subjects with mild osteoarthritis, a second cluster of members in the two-dimensional plot will represent subjects with moderate osteoarthritis, and so forth.

In some embodiments, the members of the training population are plotted against  
25 more than two principal components and a determination is made as to whether the members of the training population are clustering into groups that each uniquely represents a subgroup found in the training population. In some embodiments, principal component analysis is performed by using the *R mva* package (Anderson, 1973, *Cluster Analysis for applications*, Academic Press, New York 1973; Gordon, *Classification*, Second Edition, Chapman and Hall, CRC, 1999.). Principal component analysis is further described in  
30 Duda, *Pattern Classification*, Second Edition, 2001, John Wiley & Sons, Inc.

#### 5.14.5 NEAREST NEIGHBOR CLASSIFIER ANALYSIS

Nearest neighbor classifiers are memory-based and require no classifier to be fit. Given a query point  $x_0$ , the  $k$  training points  $x_{(r)}$ ,  $r, \dots, k$  closest in distance to  $x_0$  are

identified and then the point  $x_0$  is classified using the  $k$  nearest neighbors. Ties can be broken at random. In some embodiments, Euclidean distance in feature space is used to determine distance as:

$$d_{(i)} = \|x_{(i)} - x_o\|$$

5 Typically, when the nearest neighbor algorithm is used, the expression data used to compute the linear discriminant is standardized to have mean zero and variance 1. In the present invention, the members of the training population are randomly divided into a training set and a test set. For example, in one embodiment, two thirds of the members of the training population are placed in the training set and one third of the members of the  
10 training population are placed in the test set. A select combination of genes described in the present invention represents the feature space into which members of the test set are plotted. Next, the ability of the training set to correctly characterize the members of the test set is computed. In some embodiments, nearest neighbor computation is performed several times for a given combination of genes of the present invention. In each iteration  
15 of the computation, the members of the training population are randomly assigned to the training set and the test set. Then, the quality of the combination of genes is taken as the average of each such iteration of the nearest neighbor computation.

The nearest neighbor rule can be refined to deal with issues of unequal class priors, differential misclassification costs, and feature selection. Many of these refinements  
20 involve some form of weighted voting for the neighbors. For more information on nearest neighbor analysis, see Duda, *Pattern Classification*, Second Edition, 2001, John Wiley & Sons, Inc; and Hastie, 2001, *The Elements of Statistical Learning*, Springer, New York.

#### 5.14.6 LINEAR DISCRIMINANT ANALYSIS

Linear discriminant analysis (LDA) attempts to classify a subject into one of two  
25 categories based on certain object properties. In other words, LDA tests whether object attributes measured in an experiment predict categorization of the objects. LDA typically requires continuous independent variables and a dichotomous categorical dependent variable. In the present invention, the expression values for the select combinations of genes described in the present invention across a subset of the training population serve as  
30 the requisite continuous independent variables. The trait subgroup classification of each of the members of the training population serves as the dichotomous categorical dependent variable.



LDA seeks the linear combination of variables that maximizes the ratio of between-group variance and within-group variance by using the grouping information. Implicitly, the linear weights used by LDA depend on how the expression of a molecular marker across the training set separates in the two groups (*e.g.*, a group that has osteoarthritis and a group that does not have osteoarthritis) and how this gene expression correlates with the expression of other genes. In some embodiments, LDA is applied to the data matrix of the N members in the training sample by K genes in a combination of genes described in the present invention. Then, the linear discriminant of each member of the training population is plotted. Ideally, those members of the training population representing a first subgroup (*e.g.* those subjects that do not have osteoarthritis) will cluster into one range of linear discriminant values (*e.g.*, negative) and those member of the training population representing a second subgroup (*e.g.* those subjects that have osteoarthritis) will cluster into a second range of linear discriminant values (*e.g.*, positive). The LDA is considered more successful when the separation between the clusters of discriminant values is larger. For more information on linear discriminant analysis, see Duda, *Pattern Classification*, Second Edition, 2001, John Wiley & Sons, Inc; and Hastie, 2001, *The Elements of Statistical Learning*, Springer, New York; Venables & Ripley, 1997, *Modern Applied Statistics with s-plus*, Springer, New York.

#### 5.14.7 QUADRATIC DISCRIMINANT ANALYSIS

Quadratic discriminant analysis (QDA) takes the same input parameters and returns the same results as LDA. QDA uses quadratic equations, rather than linear equations, to produce results. LDA and QDA are interchangeable, and which to use is a matter of preference and/or availability of software to support the analysis. Logistic regression takes the same input parameters and returns the same results as LDA and QDA.

#### 5.14.8 SUPPORT VECTOR MACHINES

In some embodiments of the present invention, support vector machines (SVMs) are used to classify subjects using genes or genetic information. SVMs are a relatively new type of learning algorithm. See, for example, Cristianini and Shawe-Taylor, 2000, *An Introduction to Support Vector Machines*, Cambridge University Press, Cambridge, Boser *et al.*, 1992, "A training algorithm for optimal margin classifiers, in *Proceedings of the 5<sup>th</sup> Annual ACM Workshop on Computational Learning Theory*, ACM Press, Pittsburgh, PA, pp. 142-152; Vapnik, 1998, *Statistical Learning Theory*, Wiley, New York. When used for classification, SVMs separate a given set of binary labeled training data with a hyper-

plane that is [a maximal distance from each point using a fitting algorithm. For cases in which no linear separation is possible, SVMs can work in combination with the technique of 'kernels', which automatically realizes a non-linear mapping to a feature space. The hyper-plane found by the SVM in feature space corresponds to a non-linear decision  
5 boundary in the input space.

In one approach, when a SVM is used, the gene expression data is standardized to have mean zero and unit variance and the members of a training population are randomly divided into a training set and a test set. For example, in one embodiment, two thirds of the members of the training population are placed in the training set and one third of the  
10 members of the training population are placed in the test set. The expression values for a combination of genes is used to train the SVM. Then the ability for the trained SVM to correctly classify members in the test set is determined. In some embodiments, this computation is performed several times for a given combination of molecular markers. In each iteration of the computation, the members of the training population are randomly  
15 assigned to the training set and the test set. Then, the quality of the combination of molecular markers is taken as the average of each such iteration of the SVM computation. For more information on SVMs, see Duda, *Pattern Classification*, Second Edition, 2001, John Wiley & Sons, Inc.; Hastie, 2001, *The Elements of Statistical Learning*, Springer, New York; and Furey *et al.*, 2000, *Bioinformatics* 16, 906-914.

#### 20 **5.14.9 DECISION TREES**

In some embodiments of the present invention, decision trees are used to classify subjects using expression data for combinations of genes. Decision tree algorithms belong to the class of supervised learning algorithms. The aim of a decision tree is to induce a classifier (a tree) from real-world example data. This tree can be used to classify unseen  
25 examples which have not been used to derive the decision tree.

A decision tree is derived from training data. An example contains values for the different attributes and what class the example belongs. In the present invention, the training data is expression data for a combination of genes across the training population.

The following algorithm describes a decision tree derivation:  
30 Tree(Examples,Class,Attributes)

    Create a root node

    If all Examples have the same Class value, give the root this label

    Else if Attributes is empty label the root according to the most common value

    Else begin

Calculate the information gain for each attribute

Select the attribute A with highest information gain and make this the root attribute

For each possible value, v, of this attribute

5                   Add a new branch below the root, corresponding to  $A = v$   
                    Let  $\text{Examples}(v)$  be those examples with  $A = v$   
                    If  $\text{Examples}(v)$  is empty, make the new branch a leaf node labeled  
                    with the most common value among Examples  
                    Else let the new branch be the tree created by  
10                  Tree( $\text{Examples}(v), \text{Class}, \text{Attributes} - \{A\}$ )  
                    end

A more detailed description of the calculation of information gain is shown in the following. If the possible classes  $v_i$  of the examples have probabilities  $P(v_i)$  then the information content  $\bar{I}$  of the actual answer is given by:

15                   
$$I(P(v_1), \dots, P(v_n)) = \sum_{i=1}^n -P(v_i) \log_2 P(v_i)$$

The I- value shows how much information we need in order to be able to describe the outcome of a classification for the specific dataset used. Supposing that the dataset contains p positive (e.g. has osteoarthritis) and n negative (e.g. healthy) examples (e.g. individuals), the information contained in a correct answer is:

20                   
$$I\left(\frac{p}{p+n}, \frac{n}{p+n}\right) = -\frac{p}{p+n} \log_2 \frac{p}{p+n} - \frac{n}{p+n} \log_2 \frac{n}{p+n}$$

where  $\log_2$  is the logarithm using base two. By testing single attributes the amount of information needed to make a correct classification can be reduced. The remainder for a specific attribute A (e.g. a gene) shows how much the information that is needed can be reduced.

25                   
$$\text{Remainder}(A) = \sum_{i=1}^v \frac{p_i + n_i}{p+n} I\left(\frac{p_i}{p_i + n_i}, \frac{n_i}{p_i + n_i}\right)$$

"v" is the number of unique attribute values for attribute A in a certain dataset, "i" is a certain attribute value, "p<sub>i</sub>" is the number of examples for attribute A where the

classification is positive (e.g. cancer), " $n_i$ " is the number of examples for attribute A where the classification is negative (e.g. healthy).

The information gain of a specific attribute A is calculated as the difference between the information content for the classes and the remainder of attribute A:

5

$$Gain(A) = I\left(\frac{p}{p+n}, \frac{n}{p+n}\right) - Remainder(A)$$

The information gain is used to evaluate how important the different attributes are for the classification (how well they split up the examples), and the attribute with the highest information.

10 In general there are a number of different decision tree algorithms, many of which are described in Duda, *Pattern Classification*, Second Edition, 2001, John Wiley & Sons, Inc. Decision tree algorithms often require consideration of feature processing, impurity measure, stopping criterion, and pruning. Specific decision tree algorithms include, but are not limited to classification and regression trees (CART), multivariate decision trees, ID3, and C4.5.

15 In one approach, when a decision tree is used, the gene expression data for a select combination of genes described in the present invention across a training population is standardized to have mean zero and unit variance. The members of the training population are randomly divided into a training set and a test set. For example, in one embodiment, two thirds of the members of the training population are placed in the training set and one  
20 third of the members of the training population are placed in the test set. The expression values for a select combination of genes described in the present invention is used to construct the decision tree. Then, the ability for the decision tree to correctly classify members in the test set is determined. In some embodiments, this computation is performed several times for a given combination of molecular markers. In each iteration  
25 of the computation, the members of the training population are randomly assigned to the training set and the test set. Then, the quality of the combination of molecular markers is taken as the average of each such iteration of the decision tree computation.

#### 5.14.10 EVOLUTIONARY METHODS

30 Inspired by the process of biological evolution, evolutionary methods of classifier design employ a stochastic search for an optimal classifier. In broad overview, such methods create several classifiers - a population - from a combination of genes described

in the present invention. Each classifier varies somewhat from the other. Next, the classifiers are scored on expression data across the training population. In keeping with the analogy with biological evolution, the resulting (scalar) score is sometimes called the fitness. The classifiers are ranked according to their score and the best classifiers are retained (some portion of the total population of classifiers). Again, in keeping with biological terminology, this is called survival of the fittest. The classifiers are stochastically altered in the next generation - the children or offspring. Some offspring classifiers will have higher scores than their parent in the previous generation, some will have lower scores. The overall process is then repeated for the subsequent generation: The classifiers are scored and the best ones are retained, randomly altered to give yet another generation, and so on. In part, because of the ranking, each generation has, on average, a slightly higher score than the previous one. The process is halted when the single best classifier in a generation has a score that exceeds a desired criterion value. More information on evolutionary methods is found in, for example, Duda, Pattern Classification, Second Edition, 2001, John Wiley & Sons, Inc.

#### **5.14.11 BAGGING, BOOSTING AND THE RANDOM SUBSPACE METHOD**

Bagging, boosting and the random subspace method are combining techniques that can be used to improve weak classifiers. These techniques are designed for, and usually applied to, decision trees. In addition, Skurichina and Duin provide evidence to suggest that such techniques can also be useful in linear discriminant analysis.

In bagging, one samples the training set, generating random independent bootstrap replicates, constructs the classifier on each of these, and aggregates them by a simple majority vote in the final decision rule. See, for example, Breiman, 1996, Machine Learning 24, 123-140; and Efron & Tibshirani, An Introduction to Bootstrap, Chapman & Hall, New York, 1993.

In boosting, classifiers are constructed on weighted versions of the training set, which are dependent on previous classification results. Initially, all objects have equal weights, and the first classifier is constructed on this data set. Then, weights are changed according to the performance of the classifier. Erroneously classified objects (molecular markers in the data set) get larger weights, and the next classifier is boosted on the reweighted training set. In this way, a sequence of training sets and classifiers is obtained, which is then combined by simple majority voting or by weighted majority voting in the

final decision. See, for example, Freund & Schapire, "Experiments with a new boosting algorithm," Proceedings 13<sup>th</sup> International Conference on Machine Learning, 1996, 148-156.

To illustrate boosting, consider the case where there are two trait extremes exhibited by the population under study, extreme phenotype 1 (e.g., severe osteoarthritis), and extreme phenotype 2 (e.g., no osteoarthritis). Given a vector of predictor molecular marker  $X$  selected in step 214, a classifier  $G(X)$  produces a prediction taking one of the type values in the two value set: {extreme phenotype 1, extreme phenotype 2}. The error rate on the training sample is

$$\overline{\text{err}} = \frac{1}{N} \sum_{i=1}^N I(y_i \neq G(x_i))$$

where  $N$  is the number of subjects in the training set (the sum total of the subjects that have either extreme phenotype 1 or extreme phenotype 2). For example, if there are 49 organisms that have severe osteoarthritis and 72 organisms that have no osteoarthritis under study,  $N$  is 121.

A weak classifier is one whose error rate is only slightly better than random guessing. In the boosting algorithm, the weak classification algorithm is repeatedly applied to modified versions of the data, thereby producing a sequence of weak classifiers  $G_m(x)$ ,  $m = 1, 2, \dots, M$ . The predictions from all of the classifiers in this sequence are then combined through a weighted majority vote to produce the final prediction:

$$G(x) = \text{sign} \left( \sum_{m=1}^M \alpha_m G_m(x) \right)$$

Here  $\alpha_1, \alpha_2, \dots, \alpha_M$  are computed by the boosting algorithm and their purpose is to weigh the contribution of each respective  $G_m(x)$ . Their effect is to give higher influence to the more accurate classifiers in the sequence.

The data modifications at each boosting step consist of applying weights  $w_1, w_2, \dots, w_n$  to each of the training observations  $(x_i, y_i)$ ,  $i = 1, 2, \dots, N$ . Initially all the weights are set to  $w_i = 1/N$ , so that the first step simply trains the classifier on the data in the usual manner. For each successive iteration  $m = 2, 3, \dots, M$  the observation weights are individually modified and the classification algorithm is reapplied to the weighted observations. At stem  $m$ , those observations that were misclassified by the classifier  $G_m$ .

$G_m(x)$  induced at the previous step have their weights increased, whereas the weights are decreased for those that were classified correctly. Thus as iterations proceed, observations that are difficult to correctly classify receive ever-increasing influence. Each successive classifier is thereby forced to concentrate on those training observations that are missed by previous ones in the sequence.

The exemplary boosting algorithm is summarized as follows:

1. Initialize the observation weights  $w_i = 1/N$ ,  $i = 1, 2, \dots, N$ .
2. For  $m = 1$  to  $M$ :
  - (a) Fit a classifier  $G_m(x)$  to the training set using weights  $w_i$ .
  - (b) Compute

$$\text{err}_m = \frac{\sum_{i=1}^N w_i I(y_i \neq G_m(x_i))}{\sum_{i=1}^N w_i}$$

- (c) Compute  $\alpha_m = \log((1 - \text{err}_m) / \text{err}_m)$ .
- (d) Set  $w_i \leftarrow w_i \cdot \exp[\alpha_m \cdot I(y_i \neq G_m(x_i))]$ ,  $i = 1, 2, \dots, N$ .

3. Output  $G(x) = \text{sign} \left[ \sum_{m=1}^M \alpha_m G_m(x) \right]$

In the algorithm, the current classifier  $G_m(x)$  is induced on the weighted observations at line 2a. The resulting weighted error rate is computed at line 2b. Line 2c calculates the weight  $\alpha_m$  given to  $G_m(x)$  in producing the final classifier  $G(x)$  (line 3). The individual weights of each of the observations are updated for the next iteration at line 2d. Observations misclassified by  $G_m(x)$  have their weights scaled by a factor  $\exp(\alpha_m)$ , increasing their relative influence for inducing the next classifier  $G_{m+1}(x)$  in the sequence. In some embodiments, modifications of the Freund and Schapire, 1997, Journal of Computer and System Sciences 55, pp. 119-139, boosting method are used. See, for example, Hasti et al., The Elements of Statistical Learning, 2001, Springer, New York, Chapter 10. In some embodiments, boosting or adaptive boosting methods are used.

In some embodiments, modifications of Freund and Schapire, 1997, Journal of Computer and System Sciences 55, pp. 119-139, are used. For example, in some embodiments, feature preselection is performed using a technique such as the nonparametric scoring methods of Park et al., 2002, Pac. Symp. Biocomput. 6, 52-63. Feature preselection is a form of dimensionality reduction in which the genes that discriminate between classifications the best are selected for use in the classifier. Then, the LogitBoost procedure introduced by Friedman et al., 2000, Ann Stat 28, 337-407 is

used rather than the boosting procedure of Freund and Schapire. In some embodiments, the boosting and other classification methods of Ben-Dor et al., 2000, Journal of Computational Biology 7, 559-583 are used in the present invention. In some embodiments, the boosting and other classification methods of Freund and Schapire, 1997, Journal of Computer and System Sciences 55, 119-139, are used.

In the random subspace method, classifiers are constructed in random subspaces of the data feature space. These classifiers are usually combined by simple majority voting in the final decision rule. See, for example, Ho, "The Random subspace method for constructing decision forests," IEEE Trans Pattern Analysis and Machine Intelligence, 1998; 20(8): 832-844.

#### **5.14.12 OTHER MATHEMATICAL MODELS**

The pattern classification and statistical techniques described above are merely examples of the types of classifiers that can be used to construct a classifier. Moreover, combinations of the techniques described above can be used. Some combinations, such as the use of the combination of decision trees and boosting, have been described. However, many other combinations are possible. In addition, other techniques in the art such as Projection Pursuit and Weighted Voting can be used to construct classifiers in instances of step 216.

#### **5.15 IMPLEMENTING THE INVENTION**

The present invention provides methods and systems for screening molecular markers to identify classifiers and/or for identifying classifiers for a trait and allows for the configuration of classifiers based on combinations of a large number of molecular markers. The invention provides a selection process for reducing the potential large number of candidate molecular markers and/or combinations thereof down to a manageable number which can be evaluated in one or more mathematical models to derive one or more classifiers.

Some embodiments of the invention are preferably implemented on a computer system having a processor and a memory unit. The embodiments may be implemented as one or more software programs operating on a general purpose computer, such as a personal computer or workstation, or as dedicated special purpose hardware components. The invention allows for an identification of classifiers while reducing the system requirements. It provides techniques for consideration of a large number of potential



molecular markers in the classifier identification process with limited memory and computational requirements.

Some embodiments of the invention provide a data-driven selection of a subset of the candidate molecular markers based on their discrimination ability. Thus, it becomes possible to start out with a large group of potentially interesting molecular markers and to automatically prune the set of candidate molecular markers so that the computer system can handle the classifier identification process more efficiently, i.e. within less processing time and less memory space. This becomes more important as combinations of the molecular markers are generated in the classifier identification process and mathematical models are applied to each combination to derive classifiers, which may be a computationally expensive process, in particular when iterative techniques are applied, such as clustering, decision trees, neural networks, or evolutionary methods. Since the possible number of combinations grows almost exponentially with the number of candidate molecular markers, the processing time for the classifier evaluation become a serious problem. The pruning of candidate molecular markers allows for the consideration of two, three, four and more combinations of candidate molecular markers as basis for the classifiers. It enables the evaluation of a large number of classifiers based on molecular markers showing a promising discrimination ability and supersedes a computer resource consuming evaluation of classifiers based on molecular markers which are likely not contributing to the final trait discrimination. Thus, the invention can be implemented on a computer having less computational power and memory while the quality of the derived classifiers is maintained. On the other hand, the invention allows for the consideration of more molecular markers, which are potentially interesting for a given application (trait), with the same available system resources resulting in a possible higher classification accuracy for the derived classifiers.

The invention further provides a data-driven selection of the derived classifiers to remove classifiers and/or molecular markers which do not significantly contribute to the trait discrimination in the later application phase. This automatic pruning step evaluates the discrimination power of the individual classifiers to reduce the necessary system requirements of a diagnostic system applying the selected classifiers for the wide variety of possible medical applications. Thus, a diagnostic system configured with the identified classifiers needs less computational power and memory and may be implemented on a smaller, less expensive device. This becomes more important when the applied mathematical models are more complex and powerful. Examples of complex classifiers are

described in section 5.14 of this description and include, e.g. neural networks, nearest neighbor classifiers, decision tress, etc. The invention enables the operation of optimized combinations of complex classifiers on diagnostic devises with limited resources.

## **5.16 EMBODIMENTS OF THE INVENTION**

### **6. EXAMPLES**

Computer systems, computer program products, methods, and kits for providing health care have been disclosed. What follows are select examples that illustrate the utility and value of the present invention.

#### **6.1 EVALUATING OSTEOARTHRITIS CLASSIFIERS USING ROC CURVES**

This example demonstrates the use of an embodiment of the invention to identify individuals with mild osteoarthritis. Osteoarthritis is a form of degenerative joint disease that involves the deterioration of and changes to the cartilage and bone. In response to inflammation in and about the joint, the body responds with bony recalcification around the joint structure. This process can be slow and gradual with minimal outward symptoms, or more rapidly progressive with significant pain and discomfort. Arthritic changes can occur in response to infection and injury of the joint as well.

*Step 202 - generation of a training population.*

Blood samples were taken from 44 test individuals not having any symptoms of osteoarthritis and 50 individuals having mild osteoarthritis using the methods described in Section 5.2. A molecular marker profile resulting in data for molecular marker products of the entire human genome was measured from each of these samples. This gene expression profile data together with knowledge of which subjects have osteoarthritis and which do not constitutes the training population 44. The 44 test individuals that do not have any symptoms of osteoarthritis constitute one trait subgroup within the training population and the 50 individuals having mild osteoarthritis constitute another trait subgroup within the training population.

*Steps 204-218.*

The training population collected in step 202 was used in order to identify combinations of genes that can serve as a classifier to differentiate mild osteoarthritis from non-osteoarthritis. Thus, the classifiers developed in this example are designed to yield a positive score when they predict that a subject has mild osteoarthritis and a negative score when they predict that the subject is in the control population. Using the approach

described in Section 5.1, two specific classifiers were developed: 100000252 and 100000511. Classifier 100000252 comprises six genes and has the format:

$$\text{SCORE} = -1.839 + 0.8 \cdot \text{HSPCA} - 1.5525 \cdot \text{IKBKAP} + 1.10184 \cdot \text{IL13RA1} + 0.78923 \cdot \text{LAMC1} - 1.3974 \cdot \text{MAFB} + 1.0602 \cdot \text{PF4}.$$

5 Classifier 100000511 comprises nine genes and has the format:

$$\text{SCORE} = -4.3754 + 0.10276 \cdot \text{EGR1} - 1.1697 \cdot \text{G2AN} + 0.88767 \cdot \text{HSPCA} - 0.55785 \cdot \text{IKBKAP} + 0.94015 \cdot \text{IL13RA1} + 0.67515 \cdot \text{LAMC1} - 1.5068 \cdot \text{MAFB} + 1.0798 \cdot \text{PF4} + 0.4007 \cdot \text{TNFAIP6}.$$

10 Here, EGR1, G2AN, HSPCA, IKBKAP, IL13RA1, LAMC1, MAFB, and TNFAIP6 are genes that were identified in step 204 and validated in step 208 (Section 5.1) for their ability to discriminate between subjects that have mild osteoarthritis and subjects that do not have osteoarthritis.

#### *Step 220.*

15 To judge which classifier is more suitable as a classifier for mild osteoarthritis, a ROC curve was computed for both classifiers using the gene expression data from the 44 test individuals not having any symptoms of osteoarthritis and the 50 individuals having mild osteoarthritis. The results of the ROC computation are illustrated in Fig. 8. The area under each ROC was computed. From this computation, it was determined that the area under the ROC curve corresponding to classifier 100000252 was 0.863 whereas the area  
20 under the ROC curve corresponding to classifier 100000511 was 0.8169.

#### *Step 224.*

In some embodiments, a classifier can be constructed that includes both classifiers 100000252 and 100000511 using the voting methods described in Section 5.1. In alternative embodiments, classifier 100000252 is selected to serve as a classifier for mild  
25 osteoarthritis because it generated a larger area under the ROC curve corresponding to the classifier when tested against the training population.

## **6.2 IDENTIFIED MOLECULAR MARKERS AND MOLECULAR MARKER DATA MEASUREMENT TECHNIQUES**

30 Molecular markers useful for input into one or more steps of the invention and techniques for measuring data values of such molecular markers, can be found in United States patent application serial No. 10/601,518, filed June 20, 2003, United States patent application serial No. 10/802,875, filed March 12, 2004, United States patent application serial No. 10/809,675, filed March 25, 2004, United States patent application serial No. 10/268,730, filed October 9, 2002, United States patent application serial No. 09/477,148,

filed January 4, 2000, United States patent application serial No. 60/115,125, filed Jan. 6, 1999; and United States patent application serial No. 60/581,977, filed June 21, 2004 each of which is hereby incorporated herein by reference in its entirety.

### 6.3 CONSTRUCTION OF CLASSIFIERS FOR MANIC DEPRESSION SYNDROME

This example demonstrates the use of the claimed invention to identify biomarkers to differentiate manic depression syndrome from non manic depression syndrome and use of same. As used herein, "manic depression syndrome" (MDS) refers to a mood disorder characterized by alternating mania and depression.

#### Step 202.

Blood samples were taken from patients who were diagnosed with manic depression as defined herein. In each case, the diagnosis of manic depression was corroborated by a skilled Board certified physician. Molecular marker data was measured for each of the molecular markers of the entire human genome using blood samples from individuals who were identified as having manic depression as described herein and individuals not having manic depression. Molecular marker data for both trait subgroups were compared and gene expression profiles for each trait subpopulation compared using commercially available GeneSpring™ softwares. Hybridizations to create the gene expression profiles were done using Affymetrix® GeneChip® platforms (U133A and U133 Plus 2.0) as described herein (data not shown). Samples from patients were clustered into two trait subgroups. The first trait subgroup included patients who have manic depression and the second trait subgroup included patients who do not have manic depression (i.e., control individuals).

#### Step 204.

The Wilcox Mann Whitney rank sum test was used to identify molecular marker data that could discriminate between the control and diseased trait subgroups with a p value of  $< 0.05$ .

#### Step 206.

Molecular markers were selected from those identified with p value of  $< 0.05$  and the ability to discriminate between the control and diseased trait subgroups were confirmed using quantitative RT-PCR.

#### Steps 214-218.

Eight candidate molecular markers were chosen and an exhaustive analysis of all possible combinations of said molecular markers were considered. Molecular marker data

for each of the eight candidate molecular markers was obtained for each member of the training population and logistic regression applied to the molecular marker data so as to develop multiple classifiers. Each classifier was ranked on the basis of area under the curve and those classifiers with an ROC of greater than 0.9 chosen.

5                                   **6.4     CONSTRUCTION OF CLASSIFIERS FOR PREDICTING  
  RESPONSE TO TREATMENT**

This example demonstrates the use of an embodiment of the invention to identify a classifier for predicting the response of a subject to treatment.

*Step 202.*

10           Blood samples are taken from patients (for example patients with a disease) who are going to enter into treatment (for the disease), or who are already undergoing treatment, but at a timepoint before being able to determine how the patients will respond to treatment. In one embodiment, blood samples are taken from patients who are about to enter into a clinical trial for a new treatment, or who are in the early stages of a clinical  
15   trial. Preferably blood samples are processed so as to preserve the RNA and/or the protein products of the molecular markers. More preferably the blood samples are processed immediately, within 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 10 hours, 12, hours, 18 hours or 24 hours from having taken the blood samples from the patients.

          Subsequent to when the blood samples are taken, patients continue to be monitored  
20   for response to treatment using traditional diagnostic methods and grouped into trait subgroups on the basis of the response to treatment. For example, trait subgroups can include patients with a positive response and no negative side effects, patients with a positive response and mild side effects, patients with a negative response, patients with a toxic response, and the like. In some embodiments, the evaluation of response to treatment  
25   can take days, weeks, months or years. In some embodiments, data as described in step 202 of Section 5.1 and Section 5.3 is obtained upon processing of the blood sample. In other embodiments, data of step 202 is obtained only after a determination of response to treatment has been made. In all cases, molecular marker data is obtained from a blood sample taken at a timepoint prior to being able to determine response to treatment. Once  
30   trait subgroups are identified on the basis of response to treatment, gene expression profiles of blood samples of each trait subgroup are compared using GeneSpring™ software analysis. Hybridizations to create the gene expression profiles are done using Affymetrix® GeneChip® platforms (U133A and U133 Plus 2.0) platforms (U133A and U133 Plus 2.0) as described herein. Samples from patients are clustered into two trait

subgroups on the basis of the response to treatment. For example, one trait subgroup demonstrates a positive response to treatment whereas the second trait subgroup demonstrates a toxic response to treatment.

**Step 204.**

5        The Wilcoxon Mann Whitney rank sum test is used to identify candidate molecular markers by identifying molecular marker data that discriminates between the response and non-response trait subgroups with a p value of  $< 0.05$  to obtain candidate molecular markers.

**Step 206.**

Additional molecular marker data for the candidate molecular markers are obtained using quantitative RT-PCR. Some candidate molecular markers are removed at this point should the quantitative RT-PCR data not confirm the ability of each candidate molecular marker to discriminate as between the response trait subgroups.

Steps 214 - 218.

15       Candidate molecular marker combinations are chosen and an exhaustive analysis of  
all possible combinations of molecular markers are tested. To test all possible  
combinations of molecular markers, logistic regression is applied to the molecular marker  
data so as to develop multiple classifiers. Each classifier is ranked on the basis of area  
under the curve using the training population. Those classifiers ranking with an ROC area  
20   under curve of greater than 0.9 are further evaluated using a scoring population which is  
not the training population. Note that the blood samples used for the scoring population  
are obtained at the same time point as the blood samples used for the training population  
(e.g., at a time prior to being able to determine response to treatment).

## 6.5 CONSTRUCTION OF CLASSIFIERS FOR DETERMINING A TRAIT OF INTEREST

### 6.5.1

This example demonstrates the selection of the composition of the training population and the trait subgroups of the training population so as to result in classifiers which are useful to predict disease.

*Step 202.*

In order to predict disease, blood samples are taken from patients at a time when said patients are disease free. Preferably blood samples are processed so as to preserve the

RNA and/or the protein products of all molecular markers of the entire genome of said individual. More preferably the blood samples are processed immediately, within 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 10 hours, 12, hours, 18 hours or 24 hours from having taken the blood samples from the patients.

5           Subsequent to when the blood samples are taken, patients continue to be monitored for development of said disease using traditional diagnostic methods. At a given time point, two trait subgroups are identified, namely individuals who develop said disease of interest and individuals who do not develop said disease of interest. In some embodiments, the timepoint at which trait subgroups are identified can take days, weeks, 10 months or years. In some embodiments, data as described in step 202 of Section 5.1 and Section 5.3 is obtained upon processing of the blood sample. In other embodiments, data of step 202 is obtained only after a determination of trait subgroups has been made. In all cases, data is obtained from a blood sample taken at a timepoint prior to being able to determine disease. Once trait subgroups are identified gene expression profiles of the 15 molecular marker data of the molecular marker products from the blood samples of each trait subgroup are compared using GeneSpring™ software analysis. Hybridizations to create the gene expression profiles are done using Affymetrix® GeneChip® platforms (U133A and U133 Plus 2.0) platforms (U133A and U133 Plus 2.0) as described herein and candidate molecular markers are identified where the molecular marker data is able to 20 differentiate as between said two trait subgroups with a p value of <0.05. Said candidate molecular markers are subsequently processed as described in steps 206 to 226 to identify classifiers and molecular markers capable of predicting disease.

### 6.5.2

25           This example demonstrates the selection of the composition of the training population and the trait subgroups of the training population so as to result in classifiers which are useful to determine treatment compliance.

#### *Step 202.*

30           In order to determine treatment compliance, blood samples are taken from patients who are complying with said treatment of interest and patients who are not complying with said treatment. Preferably blood samples are processed so as to preserve the RNA and/or the protein corresponding to molecular markers of the entire genome of said individual. More preferably the blood samples are processed immediately, within 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 10 hours, 12, hours, 18 hours or 24 hours from having taken the blood samples from the patients.

Molecular marker data is obtained as described in step 202 of Section 5.1 and Section 5.3 upon processing of the blood sample. Hybridizations to create the gene expression profiles are done using Affymetrix® GeneChip® platforms (U133A and U133 Plus 2.0) platforms (U133A and U133 Plus 2.0) as described herein and candidate  
5 molecular markers are identified which differentiate as between patients who comply with said treatment of interest as compared with patients who do not comply with said treatment of interest with a p value of  $<0.05$ . Said candidate molecular markers are subsequently processed as described in steps 206 to 226 to identify classifiers and molecular markers capable of determining treatment compliance.

### 6.5.3

This example demonstrates the selection of the composition of the training population and the trait subgroups of the training population so as to result in classifiers which are useful to predict reoccurrence of disease.

#### *Step 202.*

15 In order to predict reoccurrence of disease, blood samples are taken from patients, all of whom have had a disease of interest, at a time when all of said patients are disease free. Preferably blood samples are processed so as to preserve the RNA and/or the protein corresponding to molecular markers of the entire genome of said individual. More preferably the blood samples are processed immediately, within 1 hour, 2 hours, 3 hours, 4  
20 hours, 5 hours, 6 hours, 10 hours, 12, hours, 18 hours or 24 hours from having taken the blood samples from the patients.

Subsequent to when the blood samples are taken, patients continue to be monitored for reoccurrence of said disease using traditional diagnostic methods. At a given time point, two trait subgroups are identified, namely individuals who develop reoccurrence of  
25 said disease of interest and individuals who do not develop said disease of interest. In some embodiments, the timepoint at which trait subgroups are identified can take days, weeks, months or years. In some embodiments, data as described in step 202 of Section 5.1 and Section 5.3 is obtained upon processing of the blood sample. In other embodiments, data of step 202 is obtained only after a determination of trait subgroups has  
30 been made. In all cases, data is obtained from a blood sample taken at a timepoint prior to being able to determine reoccurrence of disease. Once trait subgroups are identified molecular marker data of the molecular marker products from the blood samples of each trait subgroup are compared using GeneSpring™ software analysis. Hybridizations to create the gene expression profiles are done using Affymetrix® GeneChip® platforms



(U133A and U133 Plus 2.0) platforms (U133A and U133 Plus 2.0) as described herein and candidate molecular markers are identified whose molecular marker data differentiates as between said two trait subgroups with a p value of  $<0.05$ . Said candidate molecular markers are subsequently processed as described in steps 206 to 226 to identify classifiers and molecular markers capable of predicting reoccurrence of disease.

#### 6.5.4

This example demonstrates the use of classifiers used in series so as to diagnose a patient with a stage of disease, for example a specific stage of osteoarthritis.

We have identified previously four different stages of osteoarthritis; namely mild osteoarthritis, moderate osteoarthritis, marked osteoarthritis and severe osteoarthritis (see for example PCT patent application **WO02070737** Entitled "Compositions and Methods relating to osteoarthritis")

In some instances it is useful to determine which stage of osteoarthritis an individual has, and more importantly to confirm that said patient does not have any other stage of osteoarthritis. For example if an individual has changed their lifestyle and lost weight –to determine whether the osteoarthritis has regressed.

Classifiers of the invention are able to differentiate as between two subgroups. As such – multiple classifiers are required to specifically stage an individual.

A first classifier is developed which differentiates as between osteoarthritis and non-osteoarthritis. As described, a training population is selected comprised of two trait subgroups where said first trait subgroup is comprised of individuals having osteoarthritis and the second trait subgroup comprised of individuals not having osteoarthritis. Identification of candidate molecular markers which differentiate as between these two trait subgroups are identified as per step 202 and subsequently processed as described in steps 206 to 226 to identify classifiers and molecular markers capable of differentiating between osteoarthritis and non-osteoarthritis.

Similarly classifiers are identified which are capable of differentiating between (a) mild osteoarthritis and moderate osteoarthritis (b) moderate osteoarthritis and marked osteoarthritis (c) marked osteoarthritis and severe osteoarthritis.

In order to diagnose an individual as having marked osteoarthritis and not having mild osteoarthritis or severe osteoarthritis, a series of tests are applied. First a classifier which determines whether said patient has osteoarthritis or not is applied. Assuming said patient has osteoarthritis, a classifier is applied which determines whether said patient has either mild osteoarthritis or marked osteoarthritis. Assuming said patient has marked

osteoarthritis, a classifier is applied to determine whether said patient has marked osteoarthritis or severe osteoarthritis. The result of these series of classifiers can determine that said patient has marked osteoarthritis and does not have any other stage of osteoarthritis.

5

## 6.6 CONSTRUCTION OF CLASSIFIERS FOR DETERMINING A TRAIT OF INTEREST (OR DIFFERENTIATING BETWEEN TWO TRAITS OF INTEREST) USING THE MOLECULAR MARKERS IDENTIFIED IN ONE OF THE DISCLOSED TABLES

10 While the examples described below suggest selection of molecular markers prior to generating all combinations of classifiers from the disclosed Tables can be based on a specific measure of statistical significance (p value) as disclosed for each molecular marker (see Table G and Table H) it must be appreciated that the selection of molecular markers may also be based on any other method disclosed in this application, such as  
15 differential fold change or even a combination of selection of *p* value and differential fold change. A skilled person in the art will recognize these other methods can also be used so as to permit the selection of subsets of the molecular markers to derive lists for which a reasonable number of combinations can be tested within the limits of the computer processing capacity. The skilled person will be able to transfer the details given in this  
20 section for examples based on a *p* value evaluation to carry out the selection based on other disclosed selection methods or selection methods known to him.

**TABLE F**

Selected Table	Trait of Interest	Recommended Training Population	
		Key Trait of Members of Trait Subgroup A	Key Trait of Members of Trait Subgroup B
Table 1A	Osteoarthritis and Hypertension	Members have both Osteoarthritis and Hypertension	Members have neither Osteoarthritis nor Hypertension
Table 1B	Osteoarthritis and Obesity	Members have both Osteoarthritis and Obesity	Members have neither Osteoarthritis nor Obesity
Table 1C	Osteoarthritis and Allergies	Members have both Osteoarthritis and Allergies	Members have neither Osteoarthritis nor Allergies
Table 1D	Osteoarthritis and	Members have both	Members have

	Systemic Steroids	Osteoarthritis and are taking Systemic Steroids	neither Osteoarthritis nor are taking Steroids
Table 1E	Hypertension	Members have Hypertension	Members do not have Hypertension
Table 1F	Obesity	Members are Obese	Members are not Obese
Table 1G	Hypertension	Members have Hypertension.	Members do not have Hypertension
		Members have Hypertension and Osteoarthritis.	Members do not have Osteoarthritis
Table 1H	Hypertension and Osteoarthritis	Members have Hypertension and Osteoarthritis	Members do not have either Hypertension or Osteoarthritis
Table 1I	Obesity	Members are Obese	Members are not Obese
		Members have Obesity and Osteoarthritis	Members do not have Osteoarthritis.
Table 1J	Obesity and Osteoarthritis	Members have Osteoarthritis and are also Obese	Members do not have either Osteoarthritis and are not Obese
Table 1K	Allergies	Members have Allergies	Members do not have Allergies
		Members have Allergies and Osteoarthritis	Members do not have Osteoarthritis
Table 1L	Allergies and Osteoarthritis	Members have Allergies and Osteoarthritis	Members do not have either Allergies or Osteoarthritis
Table 1M	Systemic Steroids	Members have been taking Systemic Steroids	Members have not been taking Systemic Steroids
		Members have been taking Systemic Steroids and have Osteoarthritis	Members do not have Osteoarthritis.
Table 1N	Systemic Steroids and Osteoarthritis	Members have Osteoarthritis and have been taking Systemic Steroids	Members do not have Osteoarthritis and have not been taking systemic Steroids
Table 1O	Taking Birth Control	Members taking Birth Control	Members not taking Birth Control
	Taking Prednisone	Members taking Prednisone	Members not taking Prednisone
	Taking Hormone Replacement	Members taking Hormone	Members not taking Hormone

	Therapy	Replacement Therapy	Replacement Therapy
Table 1P	Type II Diabetes	Members have Type II Diabetes	Members do not have Type II Diabetes
Table 1Q	Hyperlipidemias	Members have Hyperlipidemia	Members do not have Hyperlipidemia
Table 1R	Lung Disease	Members have Lung Disease	Members do not have Lung Disease
Table 1S	Bladder Cancer	Members have Bladder Cancer	Members do not have Bladder Cancer
Table 1T	Early Stage Bladder Cancer	Members have Early Stage Bladder Cancer	Members do not have Bladder Cancer
		Members have Early Stage Bladder Cancer	Members do not have Early Stage Bladder Cancer
	Late Stage Bladder Cancer	Members have Late Stage Bladder Cancer	Members do not have Bladder Cancer
		Members have Late Stage Bladder Cancer	Members do not have Late Stage Bladder Cancer
Table 1U	Coronary Artery Disease (CAD)	Members have CAD	Members do not have CAD
Table 1V	Rheumatoid Arthritis (RA)	Members have RA	Members do not have RA
Table 1W	Rheumatoid Arthritis (RA)	Members have RA	Members do not have RA
Table 1X	Depression	Members have Depression	Members do not have Depression
Table 1Y	Stage of Osteoarthritis - Mild	Members have Mild OA	Members do not have OA
	Stage of Osteoarthritis – Moderate	Members have Moderate OA	Members do not have OA
	Stage of Osteoarthritis – Marked	Members have Marked OA	Members do not have OA
	Stage of Osteoarthritis – Severe	Members have Severe OA	Members do not have OA
Table 1Z	Liver Cancer	Members have Liver Cancer	Members do not have Liver Cancer
Table 1Z(b)	Liver Cancer	Members have Liver Cancer	Members do not have Liver Cancer
Table 1AA	Schizophrenia	Members have Schizophrenia	Members do not have Schizophrenia
Table 1AB	Chagas Disease	Members have Chagas Disease	Members do not have Chagas Disease
Table 1AC	Asthma	Members have	Members have OA

		Asthma and OA	
Table 1AD	Asthma	Members have Asthma	Members do not have Asthma
Table 1AE	Lung Cancer	Members have Lung Cancer	Members do not have Lung Cancer
Table 1AG	Hypertension	Members have Hypertension	Members do not have Hypertension
Table 1AH	Obesity	Members have Obesity	Members do not have Obesity
Table 1AI	Ankylosing Spondylitis	Members have Ankylosing Spondylitis	Members do not have Ankylosing Spondylitis
Table 2	Osteoarthritis	Members have Osteoarthritis	Members do not have Osteoarthritis
Table 3A	Schizophrenia or Manic Depression Syndrome (MDS)	Members have Schizophrenia	Members have MDS
Table 3B	Hepatitis or Liver Cancer	Members have Hepatitis	Members have Liver Cancer
Table 3C	Bladder Cancer or Liver Cancer	Members have Bladder Cancer	Members have Liver Cancer
Table 3D	Bladder Cancer or Testicular Cancer	Members have Bladder Cancer	Members have Testicular Cancer
Table 3E	Testicular Cancer or Kidney Cancer	Members have Testicular Cancer	Members have Kidney Cancer
Table 3F	Liver Cancer or Stomach Cancer	Members have Liver Cancer	Members have Stomach Cancer
Table 3G	Liver Cancer or Colon Cancer	Members have Liver Cancer	Members have Colon Cancer
Table 3H	Stomach Cancer or Colon Cancer	Members have Stomach Cancer	Members have Colon Cancer
Table 3I	Rheumatoid Arthritis or Osteoarthritis	Members have Rheumatoid Arthritis	Members have Osteoarthritis
Table 3K	Chagas Disease or Heart Failure	Members have Chagas Disease	Members have Heart Failure
Table 3L	Chagas Disease or Coronary Artery Disease	Members have Chagas Disease	Members have CAD
Table 3N	Coronary Artery Disease or Heart Failure	Members have CAD	Members have Heart Failure
Table 3P	Asymptomatic Chagas or Symptomatic Chagas	Members have Asymptomatic Chagas	Members have Symptomatic Chagas
Table 3Q	Alzheimer's or Schizophrenia	Members have Alzheimer's	Members have Schizophrenia
Table 3R	Alzheimer's or Manic Depression Syndrome	Members have Alzheimer's	Members have Manic Depression

Table 4A	Osteoarthritis	Members have Osteoarthritis	Members do not have Osteoarthritis
Table 4B	Osteoarthritis	Members have Osteoarthritis	Members do not have Osteoarthritis
Table 4C	Mild Osteoarthritis	Members have Mild Osteoarthritis	Members do not have Osteoarthritis
Table 4D	Mild Osteoarthritis	Members have Mild Osteoarthritis	Members do not have Osteoarthritis
Table 4E	Moderate Osteoarthritis	Members have Moderate Osteoarthritis	Members do not have Osteoarthritis
Table 4F	Moderate Osteoarthritis	Members have Moderate Osteoarthritis	Members do not have Osteoarthritis
Table 4G	Marked Osteoarthritis	Members have Marked Osteoarthritis	Members do not have Osteoarthritis
Table 4H	Marked Osteoarthritis	Members have Marked Osteoarthritis	Members do not have Osteoarthritis
Table 4I	Severe Osteoarthritis	Members have Severe Osteoarthritis	Members do not have Osteoarthritis
Table 4J	Severe Osteoarthritis	Members have Severe Osteoarthritis	Members do not have Osteoarthritis
Table 4K	Mild Osteoarthritis or Moderate Osteoarthritis	Members have Mild Osteoarthritis	Members have Moderate Osteoarthritis
Table 4L	Mild Osteoarthritis or Moderate Osteoarthritis	Members have Mild Osteoarthritis	Members have Moderate Osteoarthritis
Table 4M	Mild Osteoarthritis or Marked Osteoarthritis	Members have Mild Osteoarthritis	Members have Marked Osteoarthritis
Table 4N	Mild Osteoarthritis or Marked Osteoarthritis	Members have Mild Osteoarthritis	Members have Marked Osteoarthritis
Table 4O	Mild Osteoarthritis or Severe Osteoarthritis	Members have Mild Osteoarthritis	Members have Severe Osteoarthritis
Table 4P	Mild Osteoarthritis or Severe Osteoarthritis	Members have Mild Osteoarthritis	Members have Severe Osteoarthritis
Table 4Q	Moderate Osteoarthritis or Marked Osteoarthritis	Members have Moderate Osteoarthritis	Members have Marked Osteoarthritis
Table 4R	Moderate Osteoarthritis or Marked Osteoarthritis	Members have Moderate Osteoarthritis	Members have Marked Osteoarthritis
Table 4S	Moderate	Members have	Members have

	Osteoarthritis or Severe Osteoarthritis	Moderate Osteoarthritis	Severe Osteoarthritis
Table 4T	Moderate Osteoarthritis or Severe Osteoarthritis	Members have Moderate Osteoarthritis	Members have Severe Osteoarthritis
Table 4U	Marked Osteoarthritis or Severe Osteoarthritis	Members have Marked Osteoarthritis	Members have Severe Osteoarthritis
Table 4V	Marked Osteoarthritis or Severe Osteoarthritis	Members have Marked Osteoarthritis	Members have Severe Osteoarthritis
Table 5A	Psoriasis	Members have Psoriasis	Members do not have Psoriasis
Table 5B	Thyroid Disorder	Members have Thyroid Disorder	Members do not have Thyroid Disorder
Table 5C	Irritable Bowel Syndrome	Members have Irritable Bowel Syndrome	Members do not have Irritable Bowel Syndrome
Table 5D	Osteoporosis	Members have Osteoporosis	Members do not have Osteoporosis
Table 5E	Migraine Headaches	Members have Migraine Headaches	Members do not have Migraine Headaches
Table 5F	Eczema	Members have Eczema	Members do not have Eczema
Table 5G	NASH	Members have NASH	Members do not have NASH
Table 5H	Alzheimer's	Members have Alzheimers'	Members do not have Alzheimers'
Table 5I	Manic Depression Syndrome	Members have Manic Depression Syndrome	Members do not have Manic Depression Syndrome
Table 5J	Crohn's Colitis	Members have Crohn's Colitis	Members do not have Crohn's Colitis
Table 5K	Chronic Cholecystitis	Members have Chronic Cholecystitis	Members do not have Chronic Cholecystitis
Table 5L	Heart Failure	Members have Heart Failure	Members do not have Heart Failure
Table 5M	Cervical Cancer	Members have Cervical Cancer	Members do not have Cervical Cancer
Table 5N	Stomach Cancer	Members have Stomach Cancer	Members do not have Stomach Cancer
Table 5O	Kidney Cancer	Members have Kidney Cancer	Members do not have Kidney Cancer
Table 5P	Testicular Cancer	Members have Testicular Cancer	Members do not have Testicular

			Cancer
Table 5Q	Colon Cancer	Members have Colon Cancer	Members do not have Colon Cancer
Table 5R	Hepatitis B	Members have Hepatitis B	Members do not have Hepatitis B
Table 5S	Pancreatic Cancer	Members have Pancreatic Cancer	Members do not have Pancreatic Cancer
Table 5T	Asymptomatic Chagas	Members have Asymptomatic Chagas	Members do not have Asymptomatic Chagas
Table 5U	Symptomatic Chagas	Members have Symptomatic Chagas	Members do not have Symptomatic Chagas
Table 5V	Bladder Cancer	Members have Bladder Cancer	Members do not have Bladder Cancer
Table 6A	Cancer	Members have Cancer	Members do not have Cancer
Table 6B	Cardiovascular Disease	Members have Cardiovascular Disease	Members do not have Cardiovascular Disease
Table 6C	Neurological Disorders	Members have a Neurological Disorder	Members do not have a Neurological Disorder
Table 7A	Celebrex® or Other Cox Inhibitor	Members taking Celebrex®	Members taking non Celebrex® Cox Inhibitor
Table 7B	Celebrex®	Members taking Celebrex®	Members not taking Celebrex®
Table 7C	Vioxx®	Members taking Vioxx®	Members not taking Vioxx®
Table 7D	Vioxx® or Other Cox Inhibitor	Members taking Vioxx®	Members taking non Vioxx® Cox Inhibitor
Table 7E	NSAIDS	Members taking NSAIDS	Members not taking NSAIDS
Table 7F	Cortisone	Members taking Cortisone	Members not taking Cortisone
Table 7G	Visco Supplement	Members taking Visco Supplement	Members not taking Visco Supplement
Table 7H	Lipitor®	Members taking Lipitor®	Members not taking Lipitor®
Table 7I	Smokers	Members are Smokers	Members are not Smokers

## CONSTRUCTION OF CLASSIFIERS FOR DETERMINING A TRAIT OF INTEREST

### Steps 202-204

5 In order to identify useful classifiers for a trait of interest, for example mild osteoarthritis, one or more of the tables listed in Table F above which have the same



recommended training population can be used. Thus for example, for mild osteoarthritis, one can select one or more of Tables 1Y; 4C; 4D. These molecular markers listed resulted from application of Steps 202-204 as outlined in Figure 2A as more fully described for each Table herein. Once one or more Tables have been selected, it is helpful to select a subset of the molecular markers in the Table or Tables before proceeding to step 206. For example, combining Tables 1Y, 4C and 4D and selecting molecular markers where the molecular marker data demonstrates an ability to differentiate as between the two trait subgroups with a p value of less than 0.0001 results in 212 molecular markers. Note that p values resulting from the molecular marker data for each molecular marker identified in any of Tables 1A to 7I can be found in Tables 8A or Tables 8B below.

Table 8A identifies molecular markers via the Clone ID of the probe used to hybridize to the molecular marker products. The Clone ID corresponds to the Clone ID found in tables 1A; 1 AC; 1B; 1C; 1D; 1E; 1F; 1G; 1H; 1I; 1J; 1K; 1L; 1M; 1N; 1O; 1P; 1Q; 1R; 1V; 1X; 1Y; 1Z; 2; 4A; 4C; 4E; 4G; 4I; 4K; 4M; 4O; 4Q; 4S; 4V; 7A; 7B; 7C; 7D; 7E; 7H; and 7I (ie those Tables generated using the ChondroChip™ as outlined herein). Table 8A then identifies the corresponding Table in which the molecular marker is identified via said Clone ID. Finally the p value of the molecular marker data obtained using the ChondroChip™ is listed. Note that Table 8A is sorted first by Table number and then by p value.

Table 8B identifies molecular markers via the Affymetrix® Spot ID of the probe pair used to hybridize to the molecular marker products. The Affy Spot ID corresponds to the Affy Spot ID found in tables Tables 1AA; 1AB; 1AD; 1AE; 1AG; 1AH; 1AT; 1S; 1T; 1U; 1W; 1Z(b); 3A; 3B; 3C; 3D; 3E; 3F; 3G; 3H; 3I; 3K; 3L; 3P; 3Q; 3R; 4B; 4D; 4F; 4H; 4J; 4L; 4N; 4P; 4R; 4T; 4V; 5A; 5B; 5C; 5D; 5EE; 5F; 5G; 5H; 5I; 5J; 5K; 5L; 5M; 5N; 5O; 5P 5Q; 5R; 5S; 5T; 5U; 5V; 6A; 6B; 6C; 7F; and 7G (ie those Tables generated using the Affymetrix™ Gene Chip as outlined herein). Table 8B then identifies the corresponding Table in which the molecular marker is identified via said Affymetrix® Spot ID. Finally the p value of the molecular marker data obtained using the ChondroChip™ is listed. Note that Table 8B is sorted first by Table number and then by p value.

#### *Step 206*

For the 212 selected molecular markers – a training population is chosen having two trait subgroups where the two trait subgroups are outlined in Table F above as corresponding to the Tables used to select the molecular markers, thus in this example, the

first trait subgroup is members having mild osteoarthritis and the second trait subgroup is members not having osteoarthritis. A blood sample from each member of the training population is obtained and processed using techniques as described herein and mRNA isolated. The resulting mRNA is reverse transcribed using ABI's High Capacity cDNA

5 Archive Kit and the cDNA is then used for quantitative RT-PCR so as to collect molecular marker data for application to a logistic regression model. Amplification primers are designed for each of the 212 molecular markers. Preferably primers are chosen which amplify across an intron junction. Quantitative Real Time PCR is performed using Qiagen's QuantiTect™ Sybr Green RT-PCR kit and data corresponding to the level of  
10 RNA for each of the molecular markers  
*Steps 214 - 218.*

From the 212 candidate molecular markers selected, an exhaustive analysis of all possible combinations of molecular markers using the molecular marker data obtained using quantitative RT-PCR data is tested using logistic regression so as to develop multiple  
15 classifiers. Each classifier is ranked on the basis of area under the curve using the training population. Those classifiers ranking with an ROC area under curve of greater than 0.8 are further evaluated using a scoring population which is not the training population. Those classifiers resulting in an ROC area under the curve of greater than 0.7 as determined using the scoring population are selected. Each of the selected classifiers is comprised of a  
20 combination of molecular markers from one of Tables 1Y, 4C and 4D.

#### USE OF THE SELECTED CLASSIFIER TO DIAGNOSE AN INDIVIDUAL AS HAVING MILD OSTEOARTHRITIS.

Any of the selected classifiers can be used to diagnose an individual as having mild osteoarthritis. A blood sample from a test individual is processed using techniques as  
25 described herein to isolate mRNA. mRNA is reverse transcribed using ABI's High Capacity cDNA Archive Kit and the cDNA is then used for quantitative RT-PCR. Amplification primers are designed for each of the molecular markers in the classifier selected which amplify across an intron junction. Quantitative Real Time PCR is performed using Qiagen's QuantiTect™ Sybr Green RT-PCR kit and data corresponding to  
30 the level of RNA for each of the molecular markers of the selected classifier obtained. The data is then used in conjunction with the logistic regression classifier so as to convert the data resulting from the Quantitative RT-PCR into a single number. If the number is greater than 0 – the test individual is diagnosed as having mild osteoarthritis is the number is less than 0 the test individual is diagnosed as not having osteoarthritis.

## 7. REFERENCES CITED

All references cited herein are incorporated herein by reference in their entirety and for all purposes to the same extent as if each individual publication or patent or patent application was specifically and individually indicated to be incorporated by reference in  
5 its entirety for all purposes.

The present invention can be implemented as a computer program product that comprises a computer program mechanism embedded in a computer readable storage medium. For instance, the computer program product could contain the program modules shown in Fig. 1. These program modules may be stored on a CD-ROM, DVD, magnetic  
10 disk storage product, or any other computer readable data or program storage product. The software modules in the computer program product can also be distributed electronically, via the Internet or otherwise, by transmission of a computer data signal (in which the software modules are embedded) on a carrier wave.

Many modifications and variations of this invention can be made without departing  
15 from its spirit and scope, as will be apparent to those skilled in the art. The specific embodiments described herein are offered by way of example only, and the invention is to be limited only by the terms of the appended claims, along with the full scope of equivalents to which such claims are entitled.

Table 8A

Clone ID	TableNo.	p-value	Clone ID	TableNO.	P Value
miob8143	1A	2.14e-05	fcrb4231	1A	3.784194e-03
ncrc5844	1A	1.1356e-04	seob0755	1A	3.784194e-03
hfcr3149	1A	1.30609e-04	seoc1023	1A	3.784194e-03
fcrb3330	1A	1.71826e-04	fcrb4995	1A	4.164516e-03
ncrc9772	1A	1.71826e-04	fcrb6031	1A	4.164516e-03
fcrb2162	1A	2.24449e-04	fcrb6896	1A	4.164516e-03
ncrb8343	1A	2.55864e-04	fcrc1689	1A	4.164516e-03
fcrb4226	1A	2.91185e-04	fcrc6228	1A	4.164516e-03
seoc6182	1A	2.91185e-04	ncr7672	1A	4.164516e-03
seoa3408	1A	3.75265e-04	ncrc1885	1A	4.164516e-03
fcrb6191	1A	4.80528e-04	ncrc3544	1A	4.164516e-03
mioc1028	1A	4.80528e-04	seoa2381	1A	4.164516e-03
seob2966	1A	5.4249e-04	seob9872	1A	4.164516e-03
seoc0775	1A	5.4249e-04	fcrb2090	1A	4.577725e-03
fcrc1834	1A	7.73507e-04	hfcr0489	1A	4.577725e-03
ncrc3257	1A	7.88975e-04	miod1448	1A	4.577725e-03
ncrc2472	1A	8.68041e-04	ncr7813	1A	4.577725e-03
mioc3930	1A	1.216349e-03	ncrc9712	1A	4.577725e-03
ncr0847	1A	1.216349e-03	ncrc9855	1A	4.577725e-03
miob8947	1A	1.253946e-03	seoa0256	1A	4.577725e-03
fcrb5214	1A	1.357347e-03	seoa3555	1A	4.577725e-03
miob4037	1A	1.512638e-03	mioa0601	1A	4.9929e-03
miob8932	1A	1.512638e-03	fcrb2713	1A	5.026153e-03
fcrc0166	1A	1.683445e-03	mioa1704	1A	5.026153e-03
miob8249	1A	1.683445e-03	miob6419	1A	5.026153e-03
seob3485	1A	1.683445e-03	mioc2997	1A	5.026153e-03
seob7929	1A	1.683445e-03	mioc3127	1A	5.026153e-03
seob0154	1A	1.871074e-03	ncr7904	1A	5.026153e-03
fcrc6345	1A	2.076917e-03	ncrc5088	1A	5.026153e-03
mioa5059	1A	2.076917e-03	seoa2641	1A	5.026153e-03
fcrb4378	1A	2.302455e-03	seoa3359	1A	5.026153e-03
miod4066	1A	2.302455e-03	seob5069	1A	5.026153e-03
ncrc5091	1A	2.302455e-03	seob5213	1A	5.026153e-03
mioc0162	1A	2.452971e-03	ncr1948	1A	5.341175e-03
fcrc5516	1A	2.549264e-03	fcrb9324	1A	5.512248e-03
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ncr0615	1A	2.819017e-03	mioc2074	1A	6.038584e-03
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ncrc0729	1A	2.819017e-03	ncrc3391	1A	6.038584e-03
fcrb4572	1A	3.113486e-03	seob0168	1A	6.038584e-03
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ncrb6320	1A	3.113486e-03	mioa2377	1A	6.607863e-03
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seob2959	1A	3.113486e-03	seob9152	1A	6.607863e-03
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fcr4214	1A	3.43455e-03	fcrb5928	1A	7.222914e-03
fcrb3897	1A	3.43455e-03	fcrc6010	1A	7.222914e-03
fcrb6508	1A	3.43455e-03	fcrc6566	1A	7.222914e-03
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ncrc5780	1A	3.43455e-03	miod2330	1A	7.222914e-03
seoa0429	1A	3.43455e-03	ncr3037	1A	7.222914e-03
seoa1977	1A	3.43455e-03	ncrc9700	1A	7.222914e-03
fcr3559	1A	3.784194e-03	seoa9889	1A	7.222914e-03

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fcrb5204	1A	7.886697e-03	ncrb8385	1A	0.01
fcrc5614	1A	7.886697e-03	ncrc5949	1A	0.01
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mioc8682	1A	7.886697e-03	seoa6620	1A	0.01
ncr0212	1A	7.886697e-03	seob3141	1A	0.01
ncr7292	1A	7.886697e-03	fcr4639	1A	0.01
ncrb4331	1A	7.886697e-03	fcrb3237	1A	0.01
ncrb5595	1A	7.886697e-03	fcrb3244	1A	0.01
seoa6654	1A	7.886697e-03	fcrb4981	1A	0.01
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seob8301	1A	7.886697e-03	fcrb9686	1A	0.01
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fcrb2041	1A	8.602308e-03	miob3953	1A	0.01
mioa5085	1A	8.602308e-03	mioc0669	1A	0.01
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seoa1584	1A	8.602308e-03	ncrc4575	1A	0.01
seoa5577	1A	8.602308e-03	ncrc6127	1A	0.01
seob5319	1A	8.602308e-03	ncrc6382	1A	0.01
seob6386	1A	8.602308e-03	seoc0778	1A	0.01
seob8741	1A	8.602308e-03	seoc0924	1A	0.01
fcr1879	1A	9.372976e-03	ncrc1892	1A	0.01
fcrb1457	1A	9.372976e-03	fcr0593	1A	0.01
fcrb3644	1A	9.372976e-03	fcrb3715	1A	0.01
fcrb4388	1A	9.372976e-03	mioc4420	1A	0.01
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mioa8852	1A	9.372976e-03	ncr6343	1A	0.01
mioc1060	1A	9.372976e-03	seob5209	1A	0.01
mioc1910	1A	9.372976e-03	ncr1876	1A	0.01
miod6437	1A	9.372976e-03	miod3417	1A	0.01
ncr6072	1A	9.372976e-03	fcr4212	1A	0.01
seoa8399	1A	9.372976e-03	fcrb4413	1A	0.01
seob4197	1A	9.372976e-03	fcrb5305	1A	0.01
seob9092	1A	9.372976e-03	fcrb9253	1A	0.01
fcrb1689	1A	0.01	hfcr1189	1A	0.01
fcrb1990	1A	0.01	miod4464	1A	0.01
fcrb8542	1A	0.01	ncr3614	1A	0.01
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seob0688	1A	0.01	ncrc9562	1A	0.01
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fcrb3686	1A	0.01	seob5336	1A	0.01
fcrb5813	1A	0.01	fcrb4985	1A	0.01
fcrb6012	1A	0.01	hfcr6634	1A	0.01
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fcrc6877	1A	0.01	seob3112	1A	0.01
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mioc7084	1A	0.01
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fcrb5550	1A	0.01
fcrb6968	1A	0.01
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mioa6135	1A	0.01
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seob9898	1A	0.01
seoc0499	1A	0.01
ncr0258	1A	0.02
ncr0179	1A	0.02
fcr4902	1A	0.02
fcrb1529	1A	0.02
fcrb2044	1A	0.02
fcrb3896	1A	0.02
fcrb4890	1A	0.02
fcrb6033	1A	0.02
fcrb6432	1A	0.02
fcrc5402	1A	0.02
hfcr1141	1A	0.02
mioa8778	1A	0.02
miob7373	1A	0.02
miob8572	1A	0.02
miob9130	1A	0.02
miob9788	1A	0.02
mioc1203	1A	0.02
ncr0808	1A	0.02
ncrc9633	1A	0.02
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seoa9724	1A	0.02
seob0253	1A	0.02
seob0288	1A	0.02
seob5478	1A	0.02
hfcr3160	1A	0.02
fcr3323	1A	0.02
fcr5425	1A	0.02
fcr7295	1A	0.02
fcrb1428	1A	0.02
fcrb5389	1A	0.02
fcrc2099	1A	0.02
miob3131	1A	0.02
mioc2592	1A	0.02
mioc8153	1A	0.02
miod4938	1A	0.02
miod5122	1A	0.02
miod5785	1A	0.02
seoa6364	1A	0.02
seoa9150	1A	0.02
seob4192	1A	0.02
seob6758	1A	0.02
mioc0852	1A	0.02
fcrb2592	1A	0.02
fcrb9680	1A	0.02
hfcr4007	1A	0.02
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ncrc6795	1A	0.02
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seoc2191	1A	0.02
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fcrb5467	1A	0.02
fcrb6734	1A	0.02
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miob9671	1A	0.02
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seoa1100	1A	0.02
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seoa9389	1A	0.02
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mioc3139	1A	0.03
mioc7986	1A	0.03
miod1316	1A	0.03
miod7337	1A	0.03
ncr3811	1A	0.03
ncr9975	1A	0.03
ncrb4474	1A	0.03

ncrc5653	1A	0.03
ncrc6264	1A	0.03
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seoa6497	1A	0.03
seoa8851	1A	0.03
seob0047	1A	0.03
seob0885	1A	0.03
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fcrb4415	1A	0.03
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mioc1940	1A	0.03
miod6685	1A	0.03
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fcrb6201	1A	0.03
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seob7907	1A	0.03
seoc0149	1A	0.03
seoc0617	1A	0.03
fcrb1890	1A	0.03
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fcrb2256	1A	0.03

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fcrb5202	1A	0.03
fcrb9636	1A	0.03
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miob5675	1A	0.03
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miob8532	1A	0.03
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mioc3208	1A	0.03
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fcrc2536	1A	0.03
fcrc3993	1A	0.03
hfcr2616	1A	0.03
hfcr4423	1A	0.03
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mioa9555	1A	0.03
mioa9581	1A	0.03
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mioc1135	1A	0.03
mioc1438	1A	0.03
mioc2451	1A	0.03
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seoa3811	1A	0.03
seob1572	1A	0.03
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seob9334	1A	0.03
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fcrc4380	1A	0.04
fcrc5007	1A	0.04
fcrc5850	1A	0.04
fcrc5898	1A	0.04
mioa3331	1A	0.04
mioa3392	1A	0.04
mioa4076	1A	0.04
mioa4484	1A	0.04
miob3042	1A	0.04

miob3696	1A	0.04	seoc4316	1A	0.04
miob7209	1A	0.04	fcrc5506	1AC	6.56e-05
mioc4731	1A	0.04	fcrb7072	1AC	1.6e-04
ncr2363	1A	0.04	fcrb9202	1AC	2.5e-04
ncr8628	1A	0.04	fcrb2252	1AC	4.03e-04
ncrb2247	1A	0.04	miob2601	1AC	4.21e-04
ncrb4182	1A	0.04	ncrc7085	1AC	4.84e-04
ncrc3416	1A	0.04	miob9073	1AC	5.8e-04
seoa1575	1A	0.04	seoc2248	1AC	6.37499e-04
seob0752	1A	0.04	seoc2682	1AC	8.42e-04
seob1423	1A	0.04	miob5885	1AC	8.48e-04
seob5099	1A	0.04	ncrb1186	1AC	1.13586e-03
seob7346	1A	0.04	fcrb9147	1AC	1.49537e-03
fcr1984	1A	0.04	seob0846	1AC	1.62274e-03
fcrb2334	1A	0.04	seoa1812	1AC	1.82148e-03
fcrb8697	1A	0.04	mioa5955	1AC	2.06855e-03
fcrb9202	1A	0.04	ncrc0672	1AC	2.23855e-03
fcrc6305	1A	0.04	fcrb3040	1AC	2.56056e-03
hfcr2250	1A	0.04	fcrb6188	1AC	2.56177e-03
hfcr2314	1A	0.04	fcrc4948	1AC	2.61225e-03
hfcr3660	1A	0.04	seoc1631	1AC	2.71926e-03
mioa5404	1A	0.04	ncrc6994	1AC	2.82137e-03
miob2833	1A	0.04	mioa1701	1AC	2.82574e-03
miod2832	1A	0.04	ncrc9343	1AC	2.83011e-03
ncr5621	1A	0.04	hfcr2930	1AC	3.28473e-03
ncrb4248	1A	0.04	seoa9740	1AC	3.80488e-03
ncrc3598	1A	0.04	ncrc5919	1AC	3.81434e-03
seoa4327	1A	0.04	fcrc7051	1AC	3.82487e-03
seoa7094	1A	0.04	seoa3322	1AC	3.82543e-03
seoa9916	1A	0.04	seob4216	1AC	4.4181e-03
seob0700	1A	0.04	mioc5664	1AC	4.42431e-03
seob1345	1A	0.04	hfcr0521	1AC	4.76360e-03
seob4191	1A	0.04	mioa2475	1AC	4.76360e-03
seoc4720	1A	0.04	seob1660	1AC	4.76360e-03
ncr0291	1A	0.04	fcrb2054	1AC	4.90887e-03
fcr3936	1A	0.04	miob4441	1AC	5.11853e-03
fcr5190	1A	0.04	seob5778	1AC	5.14747e-03
fcrb1399	1A	0.04	miod0195	1AC	5.19208e-03
fcrb1523	1A	0.04	mioc1910	1AC	5.43168e-03
fcrb5702	1A	0.04	mioa8622	1AC	5.48183e-03
fcrb7051	1A	0.04	seob2085	1AC	5.48183e-03
fcrb9430	1A	0.04	miod3579	1AC	5.84188e-03
fcrc0597	1A	0.04	fcrb1697	1AC	5.88330e-03
fcrc1879	1A	0.04	mioa6585	1AC	5.89493e-03
fcrc4658	1A	0.04	seoa6495	1AC	5.89880e-03
hfcr3134	1A	0.04	mioa6991	1AC	5.9049e-03
miob0939	1A	0.04	ncrb5737	1AC	6.09961e-03
miob2656	1A	0.04	ncrc5663	1AC	6.16618e-03
miob3690	1A	0.04	ncrc1495	1AC	6.31851e-03
mioc8635	1A	0.04	seoa5838	1AC	6.31851e-03
ncr3834	1A	0.04	mioa9604	1AC	6.43571e-03
ncrb0602	1A	0.04	hfcr2963	1AC	6.54225e-03
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ncrc9557	1A	0.04	seoc3511	1AC	6.77289e-03
seoa1644	1A	0.04	miod5310	1AC	6.78152e-03
seoa3761	1A	0.04	mioa1417	1AC	7.24653e-03
seoa5214	1A	0.04	ncr3763	1AC	7.46504e-03
seoa5637	1A	0.04	seoc5209	1AC	7.50804e-03
seoa6175	1A	0.04	fcrc6989	1AC	7.55113e-03
seob0133	1A	0.04	seob7755	1AC	8.04089e-03
seob1908	1A	0.04	seob3163	1AC	8.19449e-03
seob3367	1A	0.04	miob1126	1AC	8.32195e-03
seob8742	1A	0.04	fcrb3012	1AC	8.87793e-03
seoc0284	1A	0.04	ncrc2919	1AC	8.87793e-03



mioa1337	1AC	8.89910e-03	seob8873	1AC	0.01
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miob6188	1AC	0.04	seob1319	1B	1.133188e-03
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ncr9779	1AC	0.04	seoc0778	1B	1.459426e-03
seob0572	1AC	0.04	ncr8588	1B	1.585433e-03
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miob9710	1AC	0.04	seoc1025	1B	1.866843e-03
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mioa5202	1AC	0.04	miob8932	1B	2.191755e-03
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seoa6510	1AC	0.04	ncr1780	1B	2.372265e-03
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seoa2381	1B	6.684094e-03	seoc3876	1B	0.01
mioa8778	1B	6.761728e-03	fcrc0654	1B	0.01
fcrc5690	1B	7.162145e-03	fcr4471	1B	0.01
mioa2185	1B	7.162145e-03	fcrb4345	1B	0.01
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ncrc5949	1B	7.162145e-03	fcrb7593	1B	0.01
ncrc8881	1B	7.162145e-03	fcrc2745	1B	0.01
seoa0469	1B	7.162145e-03	mioa1626	1B	0.01
seoa7917	1B	7.162145e-03	mioa9891	1B	0.01
miob3234	1B	7.260913e-03	ncr0615	1B	0.01
fcrb1990	1B	7.669588e-03	ncrc0807	1B	0.01
fcrc0637	1B	7.669588e-03	seoa5157	1B	0.01
fcrc4333	1B	7.669588e-03	seoa5685	1B	0.01
fcrc4360	1B	7.669588e-03	seoa5911	1B	0.01
mioa8851	1B	7.669588e-03	seoa9566	1B	0.01
miob9121	1B	7.669588e-03	seob7500	1B	0.01
mioc1438	1B	7.669588e-03	seoa1540	1B	0.01
ncrc0936	1B	7.669588e-03	fcr4743	1B	0.01
ncrc9867	1B	7.669588e-03	fcrb2334	1B	0.01
seoa0256	1B	7.669588e-03	fcrc6877	1B	0.01

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ncrb8821	1B	0.01
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seob1399	1B	0.01
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seob1345	1B	0.01
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seob9152	1B	0.01
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mioa7239	1B	0.01
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fcrb9963	1B	0.01
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seob3697	1B	0.02	fcrc5504	1B	0.03
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mioc4888	1B	0.04	ncrb1677	1C	0.01
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miob3072	1C	2.453741e-03	seoc1508	1C	0.01
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seoa5577	1C	3.097092e-03	fcrb3074	1C	0.01
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fcrb0775	1C	3.879912e-03	mioa1354	1C	0.01
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mioc7471	1C	3.879912e-03	mioa7957	1C	0.01
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ncrc2377	1C	0.03
ncrc6920	1C	0.03
seoa6070	1C	0.03
seob1399	1C	0.03
seob2661	1C	0.03
seob2950	1C	0.03
seob6020	1C	0.03
seob9001	1C	0.03
fcrb8762	1C	0.03
fcr4566	1C	0.03
fcrb4275	1C	0.03
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fcrb9680	1C	0.03
fcrc0180	1C	0.03
fcrc2082	1C	0.03
fcrc4734	1C	0.03
fcrc6228	1C	0.03
fcrc6888	1C	0.03
fcrc6970	1C	0.03
mioa4196	1C	0.03
mioa6832	1C	0.03
mioa9033	1C	0.03
mioa9891	1C	0.03
miob2918	1C	0.03
miob3953	1C	0.03
miob9336	1C	0.03
miod6938	1C	0.03
ncr2581	1C	0.03
ncr7292	1C	0.03
ncr8234	1C	0.03
ncrb6394	1C	0.03
ncrc0413	1C	0.03
ncrc5959	1C	0.03
ncrc6795	1C	0.03
ncrc9642	1C	0.03
seoa1615	1C	0.03
seoa2042	1C	0.03
seoa4802	1C	0.03
seoa6497	1C	0.03
seoa8501	1C	0.03
seob0321	1C	0.03
seob4160	1C	0.03
seob4782	1C	0.03
seob5711	1C	0.03
seob6836	1C	0.03
seob9241	1C	0.03
fcrb5087	1C	0.03
fcr4503	1C	0.04
fcrb3024	1C	0.04
fcrb3217	1C	0.04
fcrb3920	1C	0.04
fcrc4968	1C	0.04
fcrc5160	1C	0.04
fcrc6609	1C	0.04
hfcrc2314	1C	0.04
mioa2475	1C	0.04
mioa3290	1C	0.04
miob8711	1C	0.04
miob9052	1C	0.04
mioc3413	1C	0.04
ncr0808	1C	0.04
ncr2370	1C	0.04
ncr2994	1C	0.04
ncr3718	1C	0.04
ncr8481	1C	0.04
ncrb0328	1C	0.04
ncrb6557	1C	0.04
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ncrc0442	1C	0.04
ncrc0576	1C	0.04
ncrc1193	1C	0.04
ncrc6407	1C	0.04
seoa0913	1C	0.04
seoa1856	1C	0.04
seoa2178	1C	0.04
seoa3007	1C	0.04

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seoa3359	1C	0.04	fcr3559	1D	2.051133e-03
seoa8399	1C	0.04	fcrc2014	1D	2.051133e-03
seob3151	1C	0.04	ncr7904	1D	2.051133e-03
seob3503	1C	0.04	ncrc1049	1D	2.459013e-03
seob5574	1C	0.04	seoa3847	1D	2.459013e-03
seoc2504	1C	0.04	seob4270	1D	2.459013e-03
seoc4416	1C	0.04	seoc0775	1D	2.459013e-03
ncr1876	1C	0.04	mioc7444	1D	2.935338e-03
ncr6401	1C	0.04	ncrb8665	1D	2.935338e-03
fcrb3016	1C	0.04	seoa4056	1D	2.935338e-03
fcrb8121	1C	0.04	seoa6620	1D	2.935338e-03
fcrb9583	1C	0.04	fcrb2633	1D	3.489334e-03
fcrc4360	1C	0.04	hfcr6370	1D	3.489334e-03
hfcr2686	1C	0.04	mioa6913	1D	3.489334e-03
mioa0601	1C	0.04	ncrc0544	1D	3.489334e-03
mioa4077	1C	0.04	seob0755	1D	3.489334e-03
mioa4484	1C	0.04	seob9871	1D	4.12035e-03
mioa4753	1C	0.04	ncrb1420	1D	4.131123e-03
mioa8952	1C	0.04	ncrc8909	1D	4.131123e-03
mioa9067	1C	0.04	seoa3639	1D	4.131123e-03
miob3257	1C	0.04	seoa5444	1D	4.131123e-03
miob3552	1C	0.04	seoa9817	1D	4.131123e-03
miob4126	1C	0.04	ncr1387	1D	4.414279e-03
miob5016	1C	0.04	fcrb6005	1D	4.871761e-03
miob9441	1C	0.04	hfcr6501	1D	4.871761e-03
mioc0181	1C	0.04	mioc1783	1D	4.871761e-03
mioc3523	1C	0.04	ncr3843	1D	4.871761e-03
mioc4331	1C	0.04	ncrc1003	1D	4.871761e-03
mioc8750	1C	0.04	ncrc6623	1D	4.871761e-03
ncr0335	1C	0.04	fcrb3169	1D	5.723282e-03
ncr2408	1C	0.04	fcrb3618	1D	5.723282e-03
ncr3141	1C	0.04	hfcr2314	1D	5.723282e-03
ncr5027	1C	0.04	mioa4845	1D	5.723282e-03
ncr5065	1C	0.04	miob9905	1D	5.723282e-03
ncr8975	1C	0.04	mioc1940	1D	5.723282e-03
ncr9378	1C	0.04	mioc4190	1D	5.723282e-03
ncrc0445	1C	0.04	mioc6320	1D	5.723282e-03
ncrc1361	1C	0.04	ncr6141	1D	5.723282e-03
ncrc1567	1C	0.04	ncrc6811	1D	5.723282e-03
ncrc5150	1C	0.04	fcr1997	1D	6.698726e-03
seoa0501	1C	0.04	fcrb1420	1D	6.698726e-03
seoa1460	1C	0.04	seoa2641	1D	6.698726e-03
seoa5742	1C	0.04	seoa7669	1D	6.698726e-03
seoa7530	1C	0.04	seoa8543	1D	6.698726e-03
seob0038	1C	0.04	seob0154	1D	6.698726e-03
seob0200	1C	0.04	fcrb9655	1D	7.812173e-03
seob4127	1C	0.04	hfcr0285	1D	7.812173e-03
seob6017	1C	0.04	mioa4552	1D	7.812173e-03
seob9152	1C	0.04	mioa9821	1D	7.812173e-03
seoc1628	1C	0.04	mioc5270	1D	7.812173e-03
hfcr0521	1D	1.21e-05	ncrb4319	1D	7.812173e-03
miod4464	1D	3.22085e-04	fcrb2452	1D	9.078758e-03
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fcrb4275	1D	6.25978e-04	hfcr3209	1D	9.078758e-03
seob0089	1D	9.48395e-04	miod0777	1D	9.078758e-03
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seoa6152	1D	1.158413e-03	seoa2428	1D	9.078758e-03
fcrb5550	1D	1.408023e-03	seoa3852	1D	9.078758e-03
ncrb8385	1D	1.408023e-03	fcr1879	1D	0.01
ncrc9637	1D	1.408023e-03	fcrb6896	1D	0.01
ncrc9910	1D	1.408023e-03	mioa0252	1D	0.01
seoa5577	1D	1.703326e-03	mioa6476	1D	0.01
seob4363	1D	1.703326e-03	miod3591	1D	0.01

ncrb8605	1D	0.01	ncrc9286	1D	0.01
ncrc2080	1D	0.01	seoa3863	1D	0.01
seoa9870	1D	0.01	seoa4053	1D	0.01
ncr3237	1D	0.01	seob0442	1D	0.01
fcr3861	1D	0.01	seob0650	1D	0.01
fcr1562	1D	0.01	seob6279	1D	0.01
fcrc6470	1D	0.01	seoc0924	1D	0.01
mioa0820	1D	0.01	seoc4161	1D	0.01
mioa4318	1D	0.01	seoa8993	1D	0.01
mioc0302	1D	0.01	ncr0527	1D	0.02
miod7429	1D	0.01	fcrb7780	1D	0.02
ncrc0262	1D	0.01	mioa0494	1D	0.02
ncrc3045	1D	0.01	mioa3945	1D	0.02
seoa4040	1D	0.01	mioa5511	1D	0.02
seoa7546	1D	0.01	mioc2750	1D	0.02
seob0168	1D	0.01	mioc3066	1D	0.02
seob1526	1D	0.01	seoa6377	1D	0.02
seob6379	1D	0.01	seoa7897	1D	0.02
miod1909	1D	0.01	seoa8556	1D	0.02
fcrb1503	1D	0.01	seob1285	1D	0.02
fcrb5726	1D	0.01	seob5219	1D	0.02
fcrc1043	1D	0.01	seob7765	1D	0.02
fcrc5516	1D	0.01	seoc0149	1D	0.02
mioa3963	1D	0.01	fcrb3592	1D	0.02
mioc1590	1D	0.01	fcrb5070	1D	0.02
mioc2997	1D	0.01	fcrc4360	1D	0.02
mioc5203	1D	0.01	hfcr2629	1D	0.02
miod4129	1D	0.01	mioc0999	1D	0.02
ncrb8721	1D	0.01	miod4629	1D	0.02
ncrc0539	1D	0.01	miod6467	1D	0.02
ncrc2394	1D	0.01	ncr3189	1D	0.02
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seoa4802	1D	0.01	seoa4518	1D	0.02
seoa6118	1D	0.01	seoa5253	1D	0.02
seob9872	1D	0.01	seoa8401	1D	0.02
seoc2723	1D	0.01	seob6272	1D	0.02
fcrb4321	1D	0.01	ncr0451	1D	0.02
fcrb1731	1D	0.01	fcrb3192	1D	0.02
fcrb4788	1D	0.01	fcrb9856	1D	0.02
fcrb6012	1D	0.01	hfcr2890	1D	0.02
hfcr1811	1D	0.01	mioa3471	1D	0.02
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mioc7331	1D	0.01	miob0764	1D	0.02
ncr0213	1D	0.01	miob9130	1D	0.02
ncr1523	1D	0.01	miod6324	1D	0.02
ncr4140	1D	0.01	ncr0335	1D	0.02
ncr4522	1D	0.01	ncr4946	1D	0.02
ncr6072	1D	0.01	ncrb3314	1D	0.02
ncr7532	1D	0.01	ncrb6394	1D	0.02
seoa3105	1D	0.01	ncrc4597	1D	0.02
seoa8300	1D	0.01	seoa8486	1D	0.02
seob0752	1D	0.01	seob0085	1D	0.02
seob5319	1D	0.01	seob1319	1D	0.02
seob6206	1D	0.01	seob1345	1D	0.02
seob8301	1D	0.01	seob5528	1D	0.02
fcr0997	1D	0.01	seob6703	1D	0.02
fcr2195	1D	0.01	mioc0899	1D	0.02
fcrb1580	1D	0.01	ncrc2529	1D	0.02
fcrb5796	1D	0.01	fcr5836	1D	0.03
mioa4674	1D	0.01	fcrb6715	1D	0.03
miod6938	1D	0.01	fcrb6890	1D	0.03
ncr4647	1D	0.01	fcrb9401	1D	0.03
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ncrc3777	1D	0.01	fcrc2096	1D	0.03

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miob3308	1D	0.03	seob5213	1D	0.03
miob8702	1D	0.03	seoc1484	1D	0.03
mioc3042	1D	0.03	seoc1664	1D	0.03
mioc3746	1D	0.03	miod7351	1D	0.04
mioc4064	1D	0.03	ncr6401	1D	0.04
miod0708	1D	0.03	fcr1346	1D	0.04
miod4066	1D	0.03	fcr2218	1D	0.04
ncr1476	1D	0.03	fcrb2208	1D	0.04
ncr3713	1D	0.03	fcrb3134	1D	0.04
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seoc0780	1D	0.03	mioa8773	1D	0.04
seoc2589	1D	0.03	mioa8851	1D	0.04
seoc4288	1D	0.03	mioa9492	1D	0.04
seoc5010	1D	0.03	mioa9604	1D	0.04
mioc3296	1D	0.03	miob5646	1D	0.04
seoc3487	1D	0.03	mioc0090	1D	0.04
fcrb2350	1D	0.03	mioc1028	1D	0.04
fcrb3629	1D	0.03	mioc1088	1D	0.04
fcrb5181	1D	0.03	mioc3671	1D	0.04
fcrb9796	1D	0.03	miod4083	1D	0.04
miob3234	1D	0.03	ncr8588	1D	0.04
mioc4318	1D	0.03	ncrb6581	1D	0.04
mioc4888	1D	0.03	ncrc0413	1D	0.04
mioc5740	1D	0.03	ncrc1765	1D	0.04
mioc6374	1D	0.03	seoa3230	1D	0.04
mioc7421	1D	0.03	seoa7373	1D	0.04
miod0592	1D	0.03	seob0782	1D	0.04
miod4895	1D	0.03	seob3493	1D	0.04
ncr3297	1D	0.03	seob5478	1D	0.04
ncr3316	1D	0.03	seob6131	1D	0.04
ncrb2131	1D	0.03	seoc2131	1D	0.04
ncrc0646	1D	0.03	seoc2510	1D	0.04
ncrc5207	1D	0.03	seoc7281	1D	0.04
ncrc6242	1D	0.03	mioc1205	1D	0.04
ncrc9557	1D	0.03	ncr1526	1D	0.04
seoa1117	1D	0.03	seoc2249	1D	0.04
seoa2744	1D	0.03	fcr3664	1D	0.04
seoa3701	1D	0.03	fcr5350	1D	0.04
seoa4132	1D	0.03	fcrb1399	1D	0.04
seob6584	1D	0.03	fcrb5850	1D	0.04
seoc1480	1D	0.03	fcrc0795	1D	0.04
fcrb3857	1D	0.03	fcrc2346	1D	0.04
fcrb6639	1D	0.03	hfcrc6611	1D	0.04
fcrb7237	1D	0.03	mioa1882	1D	0.04
fcrb7321	1D	0.03	miob2668	1D	0.04
mioa5085	1D	0.03	miob3531	1D	0.04
mioa6731	1D	0.03	miob5016	1D	0.04
miob8711	1D	0.03	miob8418	1D	0.04
mioc4994	1D	0.03	mioc0902	1D	0.04
ncr0509	1D	0.03	mioc2662	1D	0.04
ncrb2092	1D	0.03	mioc3663	1D	0.04
ncrb4182	1D	0.03	mioc8063	1D	0.04
ncrb7516	1D	0.03	miod3327	1D	0.04

miod6731	1D	0.04	miod7461	1E	3.68556e-04
ncr0212	1D	0.04	fcr4699	1E	4.06485e-04
ncr0673	1D	0.04	fcrb3237	1E	4.06485e-04
ncrb8332	1D	0.04	fcrb6431	1E	4.06485e-04
ncrc0849	1D	0.04	fcrc5142	1E	4.06485e-04
ncrc6697	1D	0.04	ncr4545	1E	4.9315e-04
ncrc7040	1D	0.04	seoa5253	1E	4.9315e-04
ncrc8949	1D	0.04	fcrb3244	1E	5.42475e-04
seoa3245	1D	0.04	fcrb4345	1E	5.42475e-04
seoa5911	1D	0.04	fcrc0529	1E	5.42475e-04
seob8386	1D	0.04	hfcr3149	1E	5.42475e-04
seob8639	1D	0.04	ncr3527	1E	5.96221e-04
seoc1009	1D	0.04	ncrc2273	1E	5.96221e-04
seoc2518	1D	0.04	seob8311	1E	5.96221e-04
seoc5209	1D	0.04	seob9872	1E	5.96221e-04
fcr5509	1E	5.52e-06	fcr1328	1E	6.54736e-04
miob9748	1E	6.23e-06	fcrb2993	1E	6.54736e-04
ncr4140	1E	8.29e-06	fcrc6976	1E	6.54736e-04
miob2492	1E	1.23e-05	mioa6091	1E	6.54736e-04
miod1675	1E	1.81e-05	seoa5234	1E	6.54736e-04
mioc1107	1E	2.05e-05	mioa4564	1E	7.18387e-04
fcrc0672	1E	2.63e-05	miod7414	1E	7.18387e-04
ncrb2091	1E	2.97e-05	seob2195	1E	7.18387e-04
seob5379	1E	3.35e-05	fcrb3870	1E	7.8757e-04
miod5651	1E	5.38e-05	hfcr3922	1E	7.8757e-04
fcrb4799	1E	6.03e-05	miob1115	1E	7.8757e-04
fcrc0839	1E	6.03e-05	ncrc2670	1E	7.8757e-04
seob1766	1E	6.03e-05	fcrb3135	1E	8.62701e-04
fcr4084	1E	7.58e-05	fcrb6225	1E	8.62701e-04
fcrb9569	1E	7.58e-05	fcrb6808	1E	8.62701e-04
mioc2872	1E	8.48e-05	mioc2152	1E	8.62701e-04
miod7440	1E	8.48e-05	mioc2667	1E	8.62701e-04
seoa4802	1E	8.48e-05	miod3347	1E	8.62701e-04
ncr5168	1E	1.31557e-04	seob6446	1E	8.62701e-04
miob3982	1E	1.46458e-04	fcrb6502	1E	9.44225e-04
miod6947	1E	1.55187e-04	miod3854	1E	9.44225e-04
miob4668	1E	1.62887e-04	ncr3306	1E	9.44225e-04
ncr5055	1E	1.62887e-04	fcr4128	1E	1.032616e-03
seob7929	1E	1.62887e-04	fcrb3868	1E	1.032616e-03
ncrc3895	1E	1.80984e-04	fcrb6181	1E	1.032616e-03
seoc0780	1E	1.84e-04	mioc0824	1E	1.032616e-03
miod1195	1E	2.00899e-04	ncr8177	1E	1.032616e-03
ncrb1956	1E	2.00899e-04	fcrb4003	1E	1.128372e-03
fcrb7113	1E	2.05387e-04	ncrb0364	1E	1.128372e-03
fcrc1080	1E	2.22795e-04	fcrb3461	1E	1.232026e-03
miod7270	1E	2.22795e-04	miob6438	1E	1.232026e-03
ncrb0384	1E	2.22795e-04	mioc3492	1E	1.232026e-03
ncrc4531	1E	2.22795e-04	ncrc3842	1E	1.232026e-03
fcr5618	1E	2.35e-04	ncrc9428	1E	1.232026e-03
fcrb3217	1E	2.46844e-04	seoa4066	1E	1.232026e-03
fcrb4656	1E	2.46844e-04	seoa7249	1E	1.232026e-03
fcrc7057	1E	2.46844e-04	seoa7295	1E	1.232026e-03
mioc1440	1E	2.46844e-04	seob9282	1E	1.232026e-03
fcrb5339	1E	2.73236e-04	fcrb1691	1E	1.34414e-03
ncrc3520	1E	2.73236e-04	mioc1438	1E	1.34414e-03
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ncrc9736	1E	2.73236e-04	seob1153	1E	1.34414e-03
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ncrc2507	1E	3.02172e-04	fcrb4988	1E	1.465309e-03
seoc0416	1E	3.02172e-04	hfcr2616	1E	1.465309e-03
fcrc0487	1E	3.33867e-04	seoa2641	1E	1.465309e-03
seob4117	1E	3.33867e-04	seob3088	1E	1.465309e-03
seoa6930	1E	3.59091e-04	seob6882	1E	1.465309e-03
fcrb4391	1E	3.68556e-04	fcrb2704	1E	1.596162e-03

fcrb4077	1E	1.596162e-03	fcrb3704	1E	3.079469e-03
fcrc0775	1E	1.596162e-03	mioa2791	1E	3.079469e-03
fcrc5846	1E	1.596162e-03	mioa5586	1E	3.079469e-03
ncr4946	1E	1.596162e-03	mioc7620	1E	3.079469e-03
seoa1100	1E	1.596162e-03	ncr0615	1E	3.079469e-03
fcrb3134	1E	1.737364e-03	ncr5613	1E	3.079469e-03
fcrb6187	1E	1.737364e-03	ncrb7102	1E	3.079469e-03
mioa8679	1E	1.737364e-03	ncrc2387	1E	3.079469e-03
ncrc3391	1E	1.737364e-03	ncrc3434	1E	3.079469e-03
seoa9421	1E	1.737364e-03	seoa8268	1E	3.079469e-03
fcrc4658	1E	1.889615e-03	seob6217	1E	3.132386e-03
hfcr3921	1E	1.889615e-03	fcrb5087	1E	3.151829e-03
mioc4089	1E	1.889615e-03	fcrb6432	1E	3.332111e-03
ncrc6981	1E	1.889615e-03	fcrb9655	1E	3.332111e-03
seoa9814	1E	1.889615e-03	fcrc5290	1E	3.332111e-03
fcrb2851	1E	2.053657e-03	fcrc6888	1E	3.332111e-03
fcrc6282	1E	2.053657e-03	miob3938	1E	3.332111e-03
mioa2073	1E	2.053657e-03	miob6099	1E	3.332111e-03
mioa7617	1E	2.053657e-03	ncrc3377	1E	3.332111e-03
ncr3034	1E	2.053657e-03	ncrc6417	1E	3.332111e-03
ncrb8383	1E	2.053657e-03	seoa0302	1E	3.332111e-03
seoa3989	1E	2.053657e-03	mioc7170	1E	3.415744e-03
seob7649	1E	2.053657e-03	seob3090	1E	3.433659e-03
seob7941	1E	2.053657e-03	ncrb0060	1E	3.505099e-03
mioc0899	1E	2.084443e-03	fcrb5164	1E	3.602913e-03
fcr1312	1E	2.230269e-03	hfcr2895	1E	3.602913e-03
fcr4803	1E	2.230269e-03	miob8143	1E	3.602913e-03
fcrb5305	1E	2.230269e-03	ncr0847	1E	3.602913e-03
fcrc0112	1E	2.230269e-03	ncrb6903	1E	3.602913e-03
mioa8484	1E	2.230269e-03	ncrc6459	1E	3.602913e-03
miob7922	1E	2.230269e-03	ncrc6953	1E	3.602913e-03
ncr4673	1E	2.230269e-03	ncrc9159	1E	3.602913e-03
ncrb3498	1E	2.230269e-03	ncrc9709	1E	3.602913e-03
ncrc2888	1E	2.230269e-03	seoa1567	1E	3.602913e-03
seob0047	1E	2.230269e-03	seob7505	1E	3.602913e-03
miob8096	1E	2.267647e-03	fcr3936	1E	3.892973e-03
fcrb5253	1E	2.36428e-03	fcrb5928	1E	3.892973e-03
mioa4241	1E	2.42027e-03	fcrb9856	1E	3.892973e-03
mioa6731	1E	2.42027e-03	hfcr4349	1E	3.892973e-03
seoa1540	1E	2.42027e-03	mioa0891	1E	3.892973e-03
fcrc6916	1E	2.465032e-03	ncr3112	1E	3.892973e-03
fcrb7951	1E	2.474444e-03	ncr8827	1E	3.892973e-03
fcrb7584	1E	2.624525e-03	ncrc2701	1E	3.892973e-03
fcrc0166	1E	2.624525e-03	ncrc3436	1E	3.892973e-03
mioa3080	1E	2.624525e-03	seoa0464	1E	3.892973e-03
miob9714	1E	2.624525e-03	seoa5094	1E	3.892973e-03
miod1574	1E	2.624525e-03	seoa7250	1E	3.892973e-03
miod5369	1E	2.624525e-03	seob3462	1E	3.892973e-03
ncr5568	1E	2.624525e-03	seob7978	1E	3.892973e-03
ncrb0054	1E	2.624525e-03	fcr6748	1E	4.203441e-03
ncrc0249	1E	2.624525e-03	hfcr0501	1E	4.203441e-03
ncrc3799	1E	2.624525e-03	hfcr4423	1E	4.203441e-03
ncrc6756	1E	2.624525e-03	ncr2288	1E	4.203441e-03
ncrc9855	1E	2.624525e-03	ncr8594	1E	4.203441e-03
fcrc3998	1E	2.701854e-03	ncrb8392	1E	4.203441e-03
fcrb7700	1E	2.796352e-03	ncrc1595	1E	4.203441e-03
fcrb3342	1E	2.843941e-03	ncrc9228	1E	4.203441e-03
fcrb8080	1E	2.843941e-03	seoa1559	1E	4.203441e-03
miob8146	1E	2.843941e-03	seoa2734	1E	4.203441e-03
mioc2019	1E	2.843941e-03	seoa4167	1E	4.203441e-03
miod5184	1E	2.843941e-03	seob3517	1E	4.203441e-03
ncrc5744	1E	2.843941e-03	fcrb1890	1E	4.328333e-03
seoa9959	1E	2.843941e-03	hfcr2890	1E	4.366058e-03
fcrb5091	1E	2.938134e-03	seob3076	1E	4.392091e-03

seob1844	1E	4.448804e-03	seoa3415	1E	5.674225e-03
seob4090	1E	4.507008e-03	seoa4107	1E	5.674225e-03
fcrb4721	1E	4.535517e-03	seob0639	1E	5.674225e-03
fcrb6667	1E	4.535517e-03	seob7229	1E	5.674225e-03
fcrb7829	1E	4.535517e-03	seoa4608	1E	5.687664e-03
fcrc1971	1E	4.535517e-03	fcrb1801	1E	6.105844e-03
miob2634	1E	4.535517e-03	fcrb2080	1E	6.105844e-03
mioc0337	1E	4.535517e-03	fcrb2866	1E	6.105844e-03
ncrb8693	1E	4.535517e-03	fcrb3782	1E	6.105844e-03
ncrc3777	1E	4.535517e-03	fcrb5841	1E	6.105844e-03
ncrc4985	1E	4.535517e-03	fcrb8877	1E	6.105844e-03
ncrc9004	1E	4.535517e-03	fcrc2429	1E	6.105844e-03
ncrc9642	1E	4.535517e-03	fcrc5233	1E	6.105844e-03
ncrc9729	1E	4.535517e-03	hfcr0489	1E	6.105844e-03
seob7346	1E	4.535517e-03	mioa7140	1E	6.105844e-03
seoc4093	1E	4.535517e-03	miob3042	1E	6.105844e-03
seob4766	1E	4.631477e-03	miob6518	1E	6.105844e-03
ncrc4920	1E	4.676963e-03	miob9671	1E	6.105844e-03
seob7747	1E	4.676963e-03	mioc4319	1E	6.105844e-03
fcrb2113	1E	4.890457e-03	miod4784	1E	6.105844e-03
fcrb5118	1E	4.890457e-03	ncr3960	1E	6.105844e-03
fcrb5867	1E	4.890457e-03	ncrc2600	1E	6.105844e-03
fcrb6484	1E	4.890457e-03	ncrc5844	1E	6.105844e-03
fcrb8949	1E	4.890457e-03	ncrc9712	1E	6.105844e-03
fcrc1014	1E	4.890457e-03	seob4752	1E	6.105844e-03
miob2869	1E	4.890457e-03	seob8999	1E	6.105844e-03
miob5708	1E	4.890457e-03	seoc0705	1E	6.373843e-03
miod4518	1E	4.890457e-03	fcrb9096	1E	6.543015e-03
ncr4485	1E	4.890457e-03	fcrb1769	1E	6.565913e-03
ncr6755	1E	4.890457e-03	fcrb2256	1E	6.565913e-03
ncrc2080	1E	4.890457e-03	fcrb2713	1E	6.565913e-03
seoa8276	1E	4.890457e-03	fcrb3330	1E	6.565913e-03
seob1319	1E	4.890457e-03	fcrb6785	1E	6.565913e-03
seob4676	1E	4.890457e-03	fcrb8910	1E	6.565913e-03
ncr9108	1E	4.911008e-03	mioa2261	1E	6.565913e-03
fcrb2859	1E	5.26957e-03	mioa7957	1E	6.565913e-03
fcrb6635	1E	5.26957e-03	miob8572	1E	6.565913e-03
fcrc0481	1E	5.26957e-03	ncr3435	1E	6.565913e-03
fcrc1740	1E	5.26957e-03	ncrc1349	1E	6.565913e-03
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mioc2561	1E	5.26957e-03	seoa9389	1E	6.565913e-03
ncrb4474	1E	5.26957e-03	seob6015	1E	6.565913e-03
ncrc5553	1E	5.26957e-03	fcr1068	1E	6.596445e-03
ncrc8949	1E	5.26957e-03	seoc0068	1E	6.651586e-03
seoa4202	1E	5.26957e-03	mioa7169	1E	6.962202e-03
seoa9094	1E	5.26957e-03	fcrb1539	1E	7.055974e-03
seob2077	1E	5.26957e-03	fcrb3314	1E	7.055974e-03
seob8300	1E	5.26957e-03	hfcr3134	1E	7.055974e-03
fcr1633	1E	5.674225e-03	ncr3811	1E	7.055974e-03
fcr4469	1E	5.674225e-03	ncr4975	1E	7.055974e-03
fcr4965	1E	5.674225e-03	ncrc3887	1E	7.055974e-03
fcrb1411	1E	5.674225e-03	seoa5157	1E	7.055974e-03
fcrb2197	1E	5.674225e-03	seoa9873	1E	7.055974e-03
fcrb6171	1E	5.674225e-03	seob0817	1E	7.055974e-03
fcrc4971	1E	5.674225e-03	seob2966	1E	7.055974e-03
mioc0162	1E	5.674225e-03	seob9485	1E	7.055974e-03
ncr8337	1E	5.674225e-03	seoc1023	1E	7.055974e-03
ncr8413	1E	5.674225e-03	fcrb3227	1E	7.08625e-03
ncrc3526	1E	5.674225e-03	fcrc2775	1E	7.131424e-03
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ncrc5072	1E	5.674225e-03	fcrb7812	1E	7.483981e-03
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fcr1388	1E	7.577631e-03	mioc3045	1E	9.349172e-03
fcr7419	1E	7.577631e-03	mioc5633	1E	9.349172e-03
fcrb1492	1E	7.577631e-03	ncr0420	1E	9.349172e-03
fcrb2196	1E	7.577631e-03	ncr3163	1E	9.349172e-03
fcrb2633	1E	7.577631e-03	ncrb8352	1E	9.349172e-03
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fcrb5389	1E	7.577631e-03	seob3594	1E	9.349172e-03
fcrb7944	1E	7.577631e-03	seoc0018	1E	9.349172e-03
fcrc2573	1E	7.577631e-03	fcrc0430	1E	9.763205e-03
mioa1570	1E	7.577631e-03	hfcr3494	1E	9.763205e-03
miob7276	1E	7.577631e-03	fcrc6138	1E	9.895207e-03
miob8583	1E	7.577631e-03	miod2837	1E	9.96009e-03
ncr9378	1E	7.577631e-03	fcr1337	1E	0.01
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seoa1575	1E	7.577631e-03	fcr4214	1E	0.01
seob3513	1E	7.577631e-03	fcr6708	1E	0.01
seob5556	1E	7.577631e-03	fcrc4151	1E	0.01
seob6758	1E	7.577631e-03	mioa2374	1E	0.01
seob7419	1E	7.577631e-03	mioc1524	1E	0.01
hfcr6406	1E	7.634442e-03	miod7442	1E	0.01
ncrc3840	1E	7.795327e-03	ncr3963	1E	0.01
fcrb4868	1E	7.885744e-03	ncrc3544	1E	0.01
mioa1532	1E	7.885744e-03	ncrc4384	1E	0.01
fcrb1202	1E	8.132553e-03	ncrc6332	1E	0.01
fcrb2208	1E	8.132553e-03	miob2533	1E	0.01
fcrb6351	1E	8.132553e-03	miob9559	1E	0.01
fcrc0637	1E	8.132553e-03	fcrb7240	1E	0.01
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ncrc0457	1E	8.132553e-03	seoa0536	1E	0.01
ncrc3257	1E	8.132553e-03	hfcr0676	1E	0.01
ncrc3802	1E	8.132553e-03	fcrb6481	1E	0.01
ncrc8988	1E	8.132553e-03	ncr0927	1E	0.01
ncrc9469	1E	8.132553e-03	seob6835	1E	0.01
seob1213	1E	8.132553e-03	fcrb4238	1E	0.01
seob8029	1E	8.132553e-03	fcrc1115	1E	0.01
seob9333	1E	8.132553e-03	fcrc6877	1E	0.01
mioc1995	1E	8.415065e-03	mioa0252	1E	0.01
miod5218	1E	8.473284e-03	mioa1388	1E	0.01
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mioc4270	1E	8.722468e-03	seob4584	1E	0.01
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seoa0469	1E	8.722468e-03	seoc1876	1E	0.01
seoa1419	1E	8.722468e-03	miod1358	1E	0.01
seoa2765	1E	8.722468e-03	fcr0111	1E	0.01
seoa9930	1E	8.722468e-03	fcr3528	1E	0.01
seob5478	1E	8.722468e-03	fcrb1720	1E	0.01
seoc2447	1E	8.722468e-03	fcrb2639	1E	0.01
miod6364	1E	9.069698e-03	fcrb3896	1E	0.01
fcr6630	1E	9.098454e-03	fcrb4985	1E	0.01
fcrb1578	1E	9.349172e-03	fcrb9611	1E	0.01
fcrb3702	1E	9.349172e-03	fcrc2082	1E	0.01
mioa4245	1E	9.349172e-03	fcrc6419	1E	0.01
miob6597	1E	9.349172e-03	mioa6428	1E	0.01



miob3411	1E	0.01
miob8707	1E	0.01
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ncrc9612	1E	0.01
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seob1981	1E	0.01
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mioc7561	1E	0.01
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fcrb7703	1E	0.01
fcrc4360	1E	0.01
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mioa9025	1E	0.01
miob2341	1E	0.01
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seoc2904	1E	0.01
fcrb1573	1E	0.01

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seob0928	1E	0.01
mioc2726	1E	0.01
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fcrb5202	1E	0.01
fcrc1689	1E	0.01
fcrc5086	1E	0.01
fcrc6990	1E	0.01
hfcr6033	1E	0.01
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seob2959	1E	0.01
seob4165	1E	0.01
miod5793	1E	0.01
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fcrb6084	1E	0.01
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fcrc6228	1E	0.01
mioa4229	1E	0.01
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miob4370	1E	0.01
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fcr5425	1E	0.04	seob4075	1F	4.85728e-04
fcrb4388	1E	0.04	ncr7839	1F	5.15e-04
fcrb7885	1E	0.04	ncr3815	1F	5.17e-04
fcrc4848	1E	0.04	hfcr5942	1F	5.23e-04
fcrc5007	1E	0.04	ncr8843	1F	5.4e-04
mioa1165	1E	0.04	fcr4212	1F	5.61e-04
mioa3987	1E	0.04	fcrb2334	1F	5.71e-04
miob2067	1E	0.04	hfcr2275	1F	5.9789e-04
miob2756	1E	0.04	mioa7465	1F	6.04e-04
miob7373	1E	0.04	miob5810	1F	6.13e-04
mioc3332	1E	0.04	hfcr5864	1F	6.22e-04
mioc7542	1E	0.04	fcrc6542	1F	6.5e-04
mioc8055	1E	0.04	fcr6708	1F	6.58e-04
miod0878	1E	0.04	mioa0311	1F	6.62324e-04
ncrc0558	1E	0.04	mioc7381	1F	6.62324e-04
ncrc1103	1E	0.04	ncrb8419	1F	6.62324e-04
ncrc1247	1E	0.04	seob4105	1F	6.64e-04
ncrc3856	1E	0.04	miob1545	1F	7.28e-04
seoa2385	1E	0.04	fcrb1633	1F	7.31e-04
seoa4708	1E	0.04	mioa1276	1F	7.32964e-04
seoa8556	1E	0.04	seoa5849	1F	7.39e-04
seoa9705	1E	0.04	fcrb5467	1F	7.45e-04

seoa2385	1F	7.63e-04	seob3697	1F	1.914664e-03
seoa0418	1F	7.66e-04	fcrb2763	1F	1.928684e-03
seob8174	1F	7.87e-04	hfcr5220	1F	1.93844e-03
mioc4835	1F	8.0e-04	seob0755	1F	2.00392e-03
miob3696	1F	8.10329e-04	ncrc3650	1F	2.009196e-03
hfcr5620	1F	8.11e-04	miod3558	1F	2.053453e-03
fcr4414	1F	8.14e-04	fcrb7113	1F	2.056425e-03
fcrb4345	1F	8.23e-04	fcrb3234	1F	2.126705e-03
seob8368	1F	8.38e-04	seoc4260	1F	2.16146e-03
seob3468	1F	8.52e-04	mioa8150	1F	2.221472e-03
mioa1704	1F	8.62e-04	ncrb3369	1F	2.227846e-03
hfcr5905	1F	8.63e-04	hfcr6141	1F	2.247103e-03
seoa3392	1F	8.67e-04	seoc0068	1F	2.284571e-03
ncr2967	1F	8.69e-04	ncr3037	1F	2.287966e-03
seob4192	1F	8.69e-04	miob5888	1F	2.294368e-03
fcr4695	1F	8.71e-04	ncr6108	1F	2.294368e-03
mioa0972	1F	8.94977e-04	seob2685	1F	2.294368e-03
mioa2156	1F	9.04e-04	miob3982	1F	2.333313e-03
ncr0847	1F	9.04e-04	ncrb0513	1F	2.334478e-03
fcrc6877	1F	9.07e-04	ncr9789	1F	2.417674e-03
fcrb6465	1F	9.31e-04	ncrb0460	1F	2.498431e-03
hfcr3467	1F	9.62e-04	seoa5577	1F	2.502273e-03
mioa0364	1F	9.72e-04	ncr9933	1F	2.508241e-03
fcrc5136	1F	9.87503e-04	mioc0950	1F	2.588257e-03
ncrb5972	1F	1.013154e-03	seob4140	1F	2.589542e-03
ncrb8056	1F	1.025404e-03	mioc5603	1F	2.598809e-03
ncrb1880	1F	1.06995e-03	ncrb8437	1F	2.624852e-03
mioa4674	1F	1.08854e-03	seoc2904	1F	2.671857e-03
fcrb7324	1F	1.132955e-03	mioa1868	1F	2.739644e-03
ncrb5233	1F	1.138168e-03	mioc6417	1F	2.739644e-03
mioa0909	1F	1.189492e-03	ncr3960	1F	2.739644e-03
fcr0680	1F	1.198768e-03	ncrc3908	1F	2.739644e-03
fcrb2054	1F	1.198768e-03	seob0409	1F	2.739644e-03
miob9671	1F	1.198768e-03	seob6872	1F	2.739644e-03
fcrc6228	1F	1.250123e-03	fcrb5645	1F	2.768103e-03
mioc0699	1F	1.295875e-03	seoc2633	1F	2.782919e-03
hfcr5499	1F	1.299893e-03	seob6015	1F	2.805059e-03
fcrb2246	1F	1.302022e-03	mioc7471	1F	2.877428e-03
miod1389	1F	1.318907e-03	seoa1749	1F	2.894471e-03
fcr4902	1F	1.361678e-03	seob7465	1F	2.982853e-03
fcrb2254	1F	1.375926e-03	ncr4572	1F	2.989794e-03
seoa0353	1F	1.396441e-03	ncrc6871	1F	2.989794e-03
fcrc1803	1F	1.449724e-03	fcrb6715	1F	2.992521e-03
miob3757	1F	1.449724e-03	ncrc1411	1F	3.058649e-03
fcrb2162	1F	1.456955e-03	hfcr2930	1F	3.059881e-03
mioa3693	1F	1.472788e-03	fcr3717	1F	3.061351e-03
fcrb2744	1F	1.519135e-03	miod4019	1F	3.069637e-03
ncr6137	1F	1.552827e-03	fcrb2080	1F	3.191254e-03
fcrb6508	1F	1.580622e-03	ncr9175	1F	3.251549e-03
fcrb1397	1F	1.592036e-03	hfcr6509	1F	3.257391e-03
mioa9062	1F	1.656379e-03	mioa2292	1F	3.259973e-03
hfcr6515	1F	1.683036e-03	ncrc9850	1F	3.259973e-03
ncrc0856	1F	1.694702e-03	seob2283	1F	3.259973e-03
ncr0097	1F	1.703212e-03	seoa4066	1F	3.271732e-03
mioa9891	1F	1.746709e-03	fcrb1950	1F	3.335219e-03
seoa0536	1F	1.746709e-03	seoa9690	1F	3.339303e-03
ncr3402	1F	1.757133e-03	ncrc4985	1F	3.345513e-03
miob1830	1F	1.762715e-03	ncr7945	1F	3.346416e-03
fcrb2321	1F	1.829751e-03	hfcr6043	1F	3.358515e-03
fcrc0287	1F	1.883587e-03	seob6486	1F	3.422066e-03
fcrb6868	1F	1.914664e-03	mioa0607	1F	3.45556e-03
fcrc4722	1F	1.914664e-03	fcrc5604	1F	3.457081e-03
mioa4484	1F	1.914664e-03	seob8311	1F	3.529644e-03
miob7117	1F	1.914664e-03	miob0167	1F	3.551533e-03

ncr4503	1F	3.551533e-03	ncrc0849	1F	4.961124e-03
seoa1689	1F	3.551533e-03	seob1808	1F	4.961124e-03
seob7039	1F	3.551533e-03	seob5673	1F	4.961124e-03
fcrb2346	1F	3.631263e-03	seoa7605	1F	5.014096e-03
miob8373	1F	3.653412e-03	seob8483	1F	5.052725e-03
hfcr5473	1F	3.664884e-03	mioc4842	1F	5.15722e-03
ncr4009	1F	3.745829e-03	hfcr5522	1F	5.165867e-03
ncr8177	1F	3.751419e-03	hfcr6687	1F	5.175533e-03
miob1006	1F	3.759831e-03	fcrc2126	1F	5.191177e-03
ncr0609	1F	3.81321e-03	mioa5452	1F	5.191177e-03
seoa4829	1F	3.817245e-03	miob2093	1F	5.218484e-03
mioa2343	1F	3.845825e-03	ncrc0017	1F	5.259195e-03
ncrc6953	1F	3.845825e-03	ncrc3457	1F	5.259195e-03
fcr5425	1F	3.859974e-03	mioa8820	1F	5.382406e-03
ncr4485	1F	3.863747e-03	miod0456	1F	5.382406e-03
fcrb5639	1F	3.865895e-03	ncr3763	1F	5.382406e-03
mioa4753	1F	3.865895e-03	ncrb1670	1F	5.382406e-03
mioa9061	1F	3.865895e-03	fcrb1922	1F	5.52751e-03
miob0180	1F	3.865895e-03	fcr3269	1F	5.600028e-03
miob0189	1F	3.865895e-03	fcr2417	1F	5.638591e-03
miod0187	1F	3.865895e-03	seoa5785	1F	5.696732e-03
seoa6238	1F	3.865895e-03	seoa1089	1F	5.709807e-03
seob1133	1F	3.865895e-03	fcrb2510	1F	5.834736e-03
ncrc3030	1F	3.933089e-03	miob2227	1F	5.834736e-03
seoa8547	1F	3.94569e-03	mioc2561	1F	5.834736e-03
fcr3743	1F	3.964466e-03	seoa5691	1F	5.834736e-03
mioa8984	1F	3.964466e-03	seoc2220	1F	5.834736e-03
hfcr6375	1F	4.00567e-03	ncrc7127	1F	5.867274e-03
hfcr5956	1F	4.064802e-03	mioc2019	1F	5.891644e-03
ncr3189	1F	4.13181e-03	mioa6969	1F	5.906016e-03
seob6084	1F	4.203369e-03	seob7575	1F	6.097516e-03
fcrb6870	1F	4.204555e-03	ncrc3593	1F	6.113977e-03
mioc3958	1F	4.204555e-03	ncrb4390	1F	6.170009e-03
ncrb7482	1F	4.204555e-03	fcrb6896	1F	6.199739e-03
ncrc2780	1F	4.204555e-03	hfcr5232	1F	6.232511e-03
seoc0957	1F	4.204555e-03	ncrc5019	1F	6.25157e-03
mioc0567	1F	4.232828e-03	mioc5194	1F	6.294222e-03
fcrb5194	1F	4.288194e-03	mioa3940	1F	6.302655e-03
ncr3419	1F	4.297798e-03	fcrb2315	1F	6.316326e-03
fcrc5471	1F	4.303567e-03	fcrc6374	1F	6.320005e-03
fcrc3942	1F	4.385521e-03	mioa6721	1F	6.320005e-03
seob6701	1F	4.441698e-03	miob2466	1F	6.320005e-03
seoa4056	1F	4.458253e-03	ncr8481	1F	6.320005e-03
seob8489	1F	4.541888e-03	ncrb8605	1F	6.320005e-03
fcrb2305	1F	4.556834e-03	seoa0099	1F	6.320005e-03
mioa2185	1F	4.556834e-03	seoa0388	1F	6.320005e-03
fcr0821	1F	4.569082e-03	seoc1348	1F	6.320005e-03
fcr3823	1F	4.569082e-03	miob6099	1F	6.326637e-03
hfcr2295	1F	4.569082e-03	ncrc5079	1F	6.338658e-03
hfcr0522	1F	4.585758e-03	seob0586	1F	6.373817e-03
mioc7073	1F	4.595129e-03	seoa9889	1F	6.418044e-03
mioc2094	1F	4.690236e-03	fcr4699	1F	6.424174e-03
mioc2546	1F	4.717485e-03	fcr5019	1F	6.499398e-03
miob4307	1F	4.736268e-03	miod4269	1F	6.541189e-03
fcr7656	1F	4.778951e-03	ncrb0571	1F	6.562046e-03
ncrc9855	1F	4.823976e-03	seob7419	1F	6.640174e-03
hfcr3674	1F	4.87135e-03	mioa2774	1F	6.667082e-03
fcrb5527	1F	4.893773e-03	ncr6401	1F	6.682138e-03
fcrb2207	1F	4.928943e-03	seoa7266	1F	6.701766e-03
mioc6156	1F	4.9342e-03	seob3699	1F	6.753484e-03
fcr7095	1F	4.961124e-03	fcrb2356	1F	6.825088e-03
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miob9336	1F	4.961124e-03	fcrc2050	1F	6.840188e-03
ncrb6385	1F	4.961124e-03	hfcr5237	1F	6.840188e-03



mioa9033	1F	6.840188e-03	ncrc6846	1F	8.631293e-03
mioa9630	1F	6.840188e-03	seoa5303	1F	8.631293e-03
miob0213	1F	6.840188e-03	fcrb2133	1F	8.647588e-03
ncrc0427	1F	6.840188e-03	hfcr3149	1F	8.667419e-03
seoa6078	1F	6.840188e-03	mioc3206	1F	8.811712e-03
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fcrb5297	1F	6.946937e-03	miod5703	1F	8.861302e-03
fcrc3998	1F	6.962613e-03	ncrb1861	1F	8.882816e-03
ncrc9700	1F	6.962613e-03	mioc4420	1F	8.897141e-03
seob5260	1F	6.964546e-03	fcr5470	1F	8.900727e-03
ncrc4226	1F	6.994012e-03	miod5505	1F	8.920428e-03
seob4363	1F	7.032122e-03	fcrb2126	1F	9.199582e-03
ncr9502	1F	7.122344e-03	ncrc1578	1F	9.205415e-03
seoa0469	1F	7.129312e-03	hfcr3224	1F	9.219579e-03
mioa8851	1F	7.216452e-03	miod2232	1F	9.250174e-03
mioa5681	1F	7.217865e-03	seoa5578	1F	9.281899e-03
miob8947	1F	7.23621e-03	mioa6991	1F	9.31265e-03
seoa5151	1F	7.267712e-03	ncr7570	1F	9.31265e-03
fcr0751	1F	7.378041e-03	seoa0420	1F	9.31265e-03
fcrc3993	1F	7.389258e-03	seoa8750	1F	9.31265e-03
fcrb6620	1F	7.397348e-03	seob1526	1F	9.31265e-03
fcrc6892	1F	7.397348e-03	seob3322	1F	9.31265e-03
hfcr0011	1F	7.397348e-03	miob2668	1F	9.456576e-03
miob7970	1F	7.397348e-03	seoc1078	1F	9.467094e-03
ncrb0262	1F	7.397348e-03	seob2163	1F	9.524093e-03
ncrc1192	1F	7.397348e-03	ncr3040	1F	9.576948e-03
seoa7369	1F	7.397348e-03	ncrb3449	1F	9.579048e-03
seoc1631	1F	7.397348e-03	ncr9429	1F	9.603911e-03
mioa1417	1F	7.397472e-03	ncrc4323	1F	9.65164e-03
fcrb3079	1F	7.406491e-03	fcrc4307	1F	9.674174e-03
seoc0778	1F	7.492808e-03	seoa0137	1F	9.678908e-03
ncrb3238	1F	7.636087e-03	mioa2330	1F	9.685757e-03
mioc7662	1F	7.706037e-03	fcrb2306	1F	9.694983e-03
seoa3415	1F	7.706037e-03	hfcr5228	1F	9.697553e-03
seob0442	1F	7.706037e-03	fcrb7700	1F	9.721976e-03
ncr5975	1F	7.721088e-03	hfcr5181	1F	9.747239e-03
seoa0429	1F	7.723786e-03	ncrc3544	1F	9.74833e-03
fcrb6195	1F	7.742707e-03	ncrb8518	1F	9.75683e-03
ncr8693	1F	7.754322e-03	fcrb3192	1F	9.87471e-03
fcr1404	1F	7.795263e-03	fcr5006	1F	9.917803e-03
ncrc1871	1F	7.818883e-03	fcr5199	1F	9.921817e-03
mioa1304	1F	7.968902e-03	ncrb0200	1F	9.990439e-03
fcrb0979	1F	7.993636e-03	fcrb1477	1F	0.01
mioc3580	1F	7.993636e-03	fcrb1494	1F	0.01
seoa0486	1F	7.993636e-03	mioc7444	1F	0.01
seoc5627	1F	7.993636e-03	ncr8272	1F	0.01
fcrb6574	1F	8.038684e-03	ncrc2831	1F	0.01
mioc0161	1F	8.075165e-03	ncrc4757	1F	0.01
miod3591	1F	8.085647e-03	seoa0145	1F	0.01
hfcr5860	1F	8.106115e-03	seob0949	1F	0.01
ncrc3416	1F	8.126637e-03	seob1100	1F	0.01
miob2287	1F	8.142773e-03	seob4793	1F	0.01
seob1419	1F	8.163409e-03	seob5812	1F	0.01
fcrc0910	1F	8.3518e-03	miod2412	1F	0.01
seob2221	1F	8.390552e-03	hfcr5969	1F	0.01
seoc1785	1F	8.437195e-03	miod5622	1F	0.01
ncr3276	1F	8.480045e-03	hfcr5719	1F	0.01
seoa8902	1F	8.536355e-03	seoa8814	1F	0.01
mioa8713	1F	8.544193e-03	seoa3555	1F	0.01
fcr0224	1F	8.631293e-03	ncrb6742	1F	0.01
fcr4503	1F	8.631293e-03	miob2905	1F	0.01
mioa6093	1F	8.631293e-03	fcrb6650	1F	0.01
mioa9792	1F	8.631293e-03	fcrb1689	1F	0.01
ncr5426	1F	8.631293e-03	ncrb2092	1F	0.01

fcrc0405	1F	0.01
fcrc2014	1F	0.01
ncr5529	1F	0.01
seoa8754	1F	0.01
ncrc4444	1F	0.01
fcrb0673	1F	0.01
seoc3426	1F	0.01
ncrc0863	1F	0.01
mioc4843	1F	0.01
fcrb2713	1F	0.01
ncr8995	1F	0.01
hfcr1083	1F	0.01
ncrc1904	1F	0.01
fcrc6855	1F	0.01
mioc7731	1F	0.01
seob5099	1F	0.01
ncrc1999	1F	0.01
seoc5911	1F	0.01
miod4539	1F	0.01
fcr0018	1F	0.01
fcr0990	1F	0.01
hfcr4275	1F	0.01
mioa8767	1F	0.01
miob3426	1F	0.01
miob4756	1F	0.01
ncr2269	1F	0.01
ncrc3971	1F	0.01
seoa0470	1F	0.01
seob2994	1F	0.01
seoc6666	1F	0.01
ncr3971	1F	0.01
seob5562	1F	0.01
seoc4888	1F	0.01
ncr8357	1F	0.01
seob5579	1F	0.01
fcrb3017	1F	0.01
fcrc0686	1F	0.01
mioc1086	1F	0.01
mioa1763	1F	0.01
seob6879	1F	0.01
ncr0898	1F	0.01
ncrc3313	1F	0.01
fcrb2256	1F	0.01
seoa2162	1F	0.01
ncrc4798	1F	0.01
seob2797	1F	0.01
ncrc9867	1F	0.01
fcrb6106	1F	0.01
fcrb7703	1F	0.01
fcrc0042	1F	0.01
hfcr1189	1F	0.01
mioa8778	1F	0.01
mioa8970	1F	0.01
miob7290	1F	0.01
miob9248	1F	0.01
mioc2039	1F	0.01
miod2641	1F	0.01
ncrb5940	1F	0.01
ncrb8319	1F	0.01
seob2689	1F	0.01
seob5032	1F	0.01
seob7946	1F	0.01
ncr2926	1F	0.01
mioa3331	1F	0.01

ncr3965	1F	0.01
miod6467	1F	0.01
ncrc9343	1F	0.01
miod0807	1F	0.01
ncrb0328	1F	0.01
seob0061	1F	0.01
miod7011	1F	0.01
hfcr2693	1F	0.01
ncrc9228	1F	0.01
ncrc4903	1F	0.01
seob9480	1F	0.01
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fcrc2807	1H	3.13006e-03
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fcrc2670	1H	0.02	seoa5986	1I	1.848665e-03

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ncrc9232	1N	0.02	ncr6343	10	5.398569e-03
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hfcr2890	1N	0.02	mioa0577	10	5.937728e-03
ncr1523	1N	0.02	fcrb5123	10	6.493198e-03
fcr1562	1N	0.02	ncrc4219	10	6.586678e-03
ncrb8721	1N	0.02	fcrb9639	10	6.645906e-03
mioa2185	1N	0.02	ncrc2859	10	6.734392e-03
ncr6141	1N	0.02	fcrb7099	10	6.749149e-03
ncrc3045	1N	0.02	mioa3725	10	7.103544e-03
ncrc5207	1N	0.02	seoa3827	10	7.157172e-03
seoa1439	1N	0.02	seoc0861	10	7.27845e-03
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fcrb7780	1N	0.03	mioc3042	10	8.28488e-03
mioc2997	1N	0.03	fcrb5181	10	8.370927e-03
mioc3296	1N	0.03	mioa4845	10	8.41047e-03
ncrc0262	1N	0.03	seoa9409	10	8.522999e-03
seoc0780	1N	0.03	seoa8501	10	9.074357e-03
mioc1783	1N	0.03	seob4363	10	9.215346e-03
ncr3713	1N	0.03	ncr9175	10	9.251372e-03
ncrb3314	1N	0.03	ncrb2125	10	9.300568e-03
seob2953	1N	0.03	seob1906	10	9.52088e-03
fcrb1399	1N	0.03	seob5003	10	9.992094e-03
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seoa8993	10	3.289707e-03	fcrb6091	10	0.01
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mioc0302	10	0.04	mioc3413	1P	3.490738e-03
seob9232	10	0.04	fcrb7380	1P	3.564101e-03
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ncrb3468	10	0.04	fcrb3518	1P	3.874043e-03
fcrc6990	10	0.04	mioc1438	1P	3.954153e-03



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mioc7509	1P	5.916437e-03	miod5651	1P	0.01
miob4613	1P	5.926508e-03	seoa0044	1P	0.01
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miob4860	1Q	1.178958e-03	fcr5190	1Q	3.712298e-03
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mioa0891	1Q	1.304487e-03	mioa6738	1Q	3.712298e-03
ncrc1665	1Q	1.441864e-03	mioc2577	1Q	3.727477e-03
seoa3422	1Q	1.441864e-03	mioa8767	1Q	3.739684e-03
fcrc1019	1Q	1.484277e-03	miod5218	1Q	3.808421e-03
mioc3419	1Q	1.484277e-03	ncrc0174	1Q	3.808421e-03
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fcr2139	1Q	1.935013e-03	ncr0016	1Q	4.130421e-03
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fcrc5850	1Q	1.963872e-03	seoa6106	1Q	4.168552e-03

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seob2283	1Q	0.04	miod1450	1R	1.6e-04
seob4197	1Q	0.04	mioc8437	1R	1.73e-04
seob5379	1Q	0.04	fcrb8940	1R	2.2e-04
seob6446	1Q	0.04	seoc1311	1R	3.9e-04
seoc5612	1Q	0.04	mioc8016	1R	4.68e-04
seob0185	1Q	0.04	seob4333	1R	4.76e-04
fcr1004	1Q	0.04	fcrb5007	1R	5.07e-04
fcrb4570	1Q	0.04	ncr0429	1R	5.52e-04
mioa2013	1Q	0.04	miod5672	1R	7.23e-04
seob6572	1Q	0.04	ncrc9279	1R	7.82e-04
seoc1023	1Q	0.04	seob3982	1R	9.0e-04
miob0496	1Q	0.04	fcrb8243	1R	9.59e-04
fcrb5639	1Q	0.04	ncrb8721	1R	1.162766e-03
mioa3963	1Q	0.04	seoa8979	1R	1.319654e-03
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miob5829	1Q	0.04	seob4036	1R	1.454856e-03
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seob6541	1Q	0.04	fcrb7505	1R	1.701834e-03
seob1155	1Q	0.04	ncr7876	1R	1.750917e-03
seob7463	1Q	0.04	ncrc5758	1R	2.140366e-03
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fcrb2749	1Q	0.04	mioa5681	1R	2.965188e-03
fcrb6990	1Q	0.04	ncr3971	1R	2.965188e-03
ncr3830	1Q	0.04	fcrb1856	1R	3.128651e-03
fcrb2199	1Q	0.04	mioc2082	1R	3.266717e-03
fcrb1890	1Q	0.04	fcrb7487	1R	3.605772e-03
seob6217	1Q	0.04	seob5612	1R	3.815575e-03

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ncr2995	1R	4.406314e-03	ncrc6846	1R	0.01
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fcrb6481	1R	4.591403e-03	seob3503	1R	0.01
miob4864	1R	5.008048e-03	seoc0203	1R	0.01
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seob9124	1R	5.140962e-03	ncr6197	1R	0.01
fcrc0302	1R	5.314391e-03	fcr0469	1R	0.01
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fcr3973	1R	5.680774e-03	seob0999	1R	0.01
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seob4539	1R	5.985149e-03	ncrb5227	1R	0.01
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miob4348	1R	6.431377e-03	fcrb5840	1R	0.01
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fcrc7180	1R	6.981505e-03	miob2834	1R	0.01
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miob4346	1R	7.267233e-03	ncrc9010	1R	0.01
miob9073	1R	7.267233e-03	seoa7094	1R	0.01
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seob4726	1R	7.267233e-03	ncr6893	1R	0.01
seoc0438	1R	7.267233e-03	fcrb2800	1R	0.01
seoc2131	1R	7.267233e-03	fcr5470	1R	0.01
mioc2887	1R	7.625229e-03	mioc1978	1R	0.01
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fcrb3550	1R	8.107057e-03	fcrb7430	1R	0.01
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miob9495	1R	8.352358e-03	ncr5890	1R	0.01
mioa3428	1R	8.522496e-03	ncr7097	1R	0.01
fcr3033	1R	8.949232e-03	ncrb7635	1R	0.01
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fcrb2197	1R	0.01	seob7047	1R	0.02
fcrb5867	1R	0.01	fcrb2159	1R	0.02
fcrb7723	1R	0.01	seoa4284	1R	0.02
mioc3906	1R	0.01	seob4424	1R	0.02
fcrc5154	1R	0.01	ncrc9483	1R	0.02
hfcr3207	1R	0.01	seoa5766	1R	0.02
ncrc9525	1R	0.01	fcr1068	1R	0.02
fcr0553	1R	0.02	ncrc5553	1R	0.02
fcrb8623	1R	0.02	seoa7897	1R	0.02
fcrb9602	1R	0.02	seob5730	1R	0.02
fcrc5126	1R	0.02	seob9122	1R	0.02
hfcr5719	1R	0.02	seob6415	1R	0.02
mioa4484	1R	0.02	fcr0793	1R	0.02
mioc2021	1R	0.02	fcrc5136	1R	0.02
mioc8412	1R	0.02	mioa0890	1R	0.02
miod1937	1R	0.02	mioa2528	1R	0.02
ncrb0487	1R	0.02	miob2668	1R	0.02
ncrb0602	1R	0.02	miob3942	1R	0.02

ncr9779	1R	0.02	fcrc5850	1R	0.03
ncrb0367	1R	0.02	mioa6585	1R	0.03
seob0949	1R	0.02	mioc2961	1R	0.03
seob9871	1R	0.02	miod1885	1R	0.03
fcr1608	1R	0.02	ncrc5232	1R	0.03
fcr3181	1R	0.02	seoa7366	1R	0.03
seoc1957	1R	0.02	seoa8609	1R	0.03
ncrc3526	1R	0.02	seob3545	1R	0.03
ncr6811	1R	0.02	seob6020	1R	0.03
fcrb6410	1R	0.02	seob6680	1R	0.03
fcrb1924	1R	0.02	seoa5525	1R	0.03
seoa6387	1R	0.02	mioc7296	1R	0.03
seoa0221	1R	0.02	seob6132	1R	0.03
ncrc1374	1R	0.02	seoc3269	1R	0.03
mioa0707	1R	0.02	miob8698	1R	0.03
hfcr0543	1R	0.02	mioc4769	1R	0.03
fcrc4390	1R	0.02	ncrb3638	1R	0.03
fcr3539	1R	0.02	seob1238	1R	0.03
fcr5536	1R	0.02	fcr2729	1R	0.03
fcrb2460	1R	0.02	mioc3523	1R	0.03
fcrb3169	1R	0.02	ncrc9168	1R	0.03
fcrb5440	1R	0.02	fcrb2484	1R	0.03
fcrb7885	1R	0.02	fcrb8808	1R	0.03
fcrc0042	1R	0.02	seob8639	1R	0.03
fcrc3998	1R	0.02	miob9678	1R	0.03
fcrc6560	1R	0.02	hfcr0383	1R	0.03
hfcr3446	1R	0.02	fcr3620	1R	0.03
hfcr6322	1R	0.02	fcrb3201	1R	0.03
mioa1055	1R	0.02	ncrc0744	1R	0.03
mioa6102	1R	0.02	seoc2218	1R	0.03
mioa6567	1R	0.02	fcrb2094	1R	0.03
mioc4552	1R	0.02	fcrb6785	1R	0.03
ncr3588	1R	0.02	mioc7904	1R	0.03
ncrb3768	1R	0.02	ncr3434	1R	0.03
ncrb5837	1R	0.02	ncrb8385	1R	0.03
ncrb8102	1R	0.02	ncrc2868	1R	0.03
ncrc2807	1R	0.02	ncrb8790	1R	0.03
seoa0388	1R	0.02	fcr7415	1R	0.03
seoa6510	1R	0.02	fcrb4932	1R	0.03
seob9353	1R	0.02	fcrb4995	1R	0.03
seoc2510	1R	0.02	fcrb5688	1R	0.03
seob5064	1R	0.02	fcrc5713	1R	0.03
fcr4568	1R	0.02	hfcr4007	1R	0.03
seoa2385	1R	0.02	mioa0874	1R	0.03
seoa7077	1R	0.02	miob1789	1R	0.03
fcrb8891	1R	0.02	mioc0699	1R	0.03
miob8487	1R	0.02	mioc2587	1R	0.03
fcrb4918	1R	0.02	mioc2728	1R	0.03
miob2466	1R	0.02	mioc7895	1R	0.03
seob1100	1R	0.02	ncr6232	1R	0.03
fcrc4846	1R	0.02	ncr7923	1R	0.03
fcr2935	1R	0.02	ncrb2013	1R	0.03
seob8839	1R	0.02	ncrb3444	1R	0.03
fcrc0839	1R	0.02	ncrb4402	1R	0.03
ncrc2531	1R	0.02	ncrc1192	1R	0.03
fcrb4504	1R	0.02	ncrc4411	1R	0.03
fcrc5092	1R	0.02	seoa4167	1R	0.03
seob8311	1R	0.02	seoa5366	1R	0.03
seoc2518	1R	0.02	seob3523	1R	0.03
seoa0010	1R	0.02	seob8242	1R	0.03
fcr2293	1R	0.03	seoc4960	1R	0.03
fcrb6141	1R	0.03	seoc5134	1R	0.03
fcrb6817	1R	0.03	mioc1049	1R	0.03
fcrc5113	1R	0.03	mioc3726	1R	0.03



mioa3084	1R	0.03
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ncr8199	1R	0.03
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fcrb5199	1R	0.03
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fcr2684	1R	0.03
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mioa0820	1R	0.03
fcrb5114	1R	0.03
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seoa5090	1R	0.03
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fcr3053	1R	0.03
fcrb5564	1R	0.03
fcrb8870	1R	0.03
fcrc2280	1R	0.03
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fcrb2292	1R	0.03
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ncr7151	1R	0.03
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seob5458	1R	0.03
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mioa1971	1R	0.03
mioc9206	1R	0.03
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seob6139	1R	0.03
ncr9933	1R	0.03
miod7326	1R	0.03
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mioa8622	1R	0.04
fcr3379	1R	0.04
fcrb9151	1R	0.04
fcrb9620	1R	0.04
hfcr3467	1R	0.04
hfcr3615	1R	0.04
hfcr5237	1R	0.04
mioa0891	1R	0.04
mioa5531	1R	0.04
mioa8820	1R	0.04
mioc2828	1R	0.04
ncr1712	1R	0.04
ncr1768	1R	0.04
ncr7595	1R	0.04
ncrb3373	1R	0.04
ncrb7211	1R	0.04
seoa0207	1R	0.04
seoa5575	1R	0.04
seob6812	1R	0.04
fcrc2745	1R	0.04
mioa0245	1R	0.04
mioa0763	1R	0.04
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mioc6412	1R	0.04
ncr3339	1R	0.04
mioc3716	1R	0.04
mioc7668	1R	0.04
fcr4272	1R	0.04
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fcrc5482	1R	0.04
seoc5228	1R	0.04
miod3205	1R	0.04
seob9368	1R	0.04
fcrc2050	1R	0.04
fcrc4157	1R	0.04
mioc0301	1R	0.04
ncrc1326	1R	0.04
seoa9363	1R	0.04
seob4804	1R	0.04
fcrb2124	1R	0.04
fcr3957	1R	0.04
fcr0253	1R	0.04
fcr1562	1R	0.04
fcr5474	1R	0.04
fcrc5309	1R	0.04
hfcr6700	1R	0.04
mioa0601	1R	0.04
mioa8774	1R	0.04
miob4368	1R	0.04
mioc3127	1R	0.04
mioc6385	1R	0.04
mioc8635	1R	0.04
ncr8481	1R	0.04
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ncrb7167	1R	0.04
ncrc0856	1R	0.04
ncrc5738	1R	0.04
seoa4670	1R	0.04
seob1574	1R	0.04
seob4105	1R	0.04
seob4498	1R	0.04
seoc0513	1R	0.04
fcr4214	1R	0.04
fcrb6522	1R	0.04

ncrc2443	1R	0.04	seoc2030	1R	0.04
ncr6637	1R	0.04	seoa1644	1V	2.4e-07
fcrb5679	1R	0.04	fcrb4985	1V	7.42e-07
seob6028	1R	0.04	seob3307	1V	8.48e-06
seoa0238	1R	0.04	seob2775	1V	1.28e-05
fcrc0559	1R	0.04	fcrb5214	1V	2.5e-05
ncrc0803	1R	0.04	fcrb8489	1V	2.68e-05
mioc6925	1R	0.04	mioc6211	1V	3.64e-05
hfcr3224	1R	0.04	miod6234	1V	3.66e-05
ncrc0863	1R	0.04	hfcr3180	1V	4.19e-05
miob4760	1R	0.04	fcrb2256	1V	4.65e-05
seob5954	1R	0.04	ncrc9436	1V	5.3e-05
seoa5302	1R	0.04	fcrb4981	1V	5.58e-05
fcrb6301	1R	0.04	seoa9997	1V	6.35e-05
ncrc0922	1R	0.04	seoc0009	1V	6.35e-05
fcrc5007	1R	0.04	miob9805	1V	7.39e-05
fcrc1313	1R	0.04	seoa0099	1V	8.58e-05
mioc0240	1R	0.04	seob4197	1V	8.72e-05
miod7099	1R	0.04	fcr5836	1V	9.95e-05
ncrc0341	1R	0.04	fcrc5604	1V	1.06e-04
fcr0343	1R	0.04	mioa4229	1V	1.08e-04
fcr2182	1R	0.04	fcrb4781	1V	1.15081e-04
fcrb1604	1R	0.04	fcrb2137	1V	1.21e-04
fcrb1854	1R	0.04	seob2937	1V	1.23e-04
fcrc4005	1R	0.04	fcrb3966	1V	1.27e-04
hfcr3067	1R	0.04	seob2938	1V	1.52e-04
hfcr3070	1R	0.04	hfcr2287	1V	1.53205e-04
hfcr4170	1R	0.04	miod4564	1V	1.53205e-04
hfcr4275	1R	0.04	seoa1460	1V	1.53205e-04
mioa2165	1R	0.04	ncrc5019	1V	1.72e-04
mioa5902	1R	0.04	hfcr5969	1V	1.76303e-04
mioa8452	1R	0.04	mioa2993	1V	2.02535e-04
mioa8594	1R	0.04	miod5505	1V	2.02535e-04
miob5119	1R	0.04	fcrb5123	1V	2.14e-04
miod4407	1R	0.04	hfcr2844	1V	2.22e-04
miod7367	1R	0.04	miod7099	1V	2.26e-04
ncr4612	1R	0.04	fcr5339	1V	2.32274e-04
ncr5975	1R	0.04	miob9652	1V	2.32274e-04
ncr8725	1R	0.04	seoa1883	1V	2.32274e-04
ncrb0090	1R	0.04	seoa5652	1V	2.32274e-04
ncrb3011	1R	0.04	seob5100	1V	2.32274e-04
ncrb7376	1R	0.04	ncrc5150	1V	2.45e-04
ncrc1653	1R	0.04	seob6217	1V	2.45e-04
ncrc6129	1R	0.04	seob7500	1V	2.45e-04
ncrc7171	1R	0.04	mioc0121	1V	2.45493e-04
seoa0064	1R	0.04	seob4306	1V	2.49e-04
seoa6238	1R	0.04	seob2950	1V	2.65e-04
seoa8266	1R	0.04	ncr2892	1V	2.65933e-04
seob8854	1R	0.04	ncrb3980	1V	2.65933e-04
seoc1539	1R	0.04	seoa6178	1V	2.65933e-04
seoc1764	1R	0.04	seoc3519	1V	2.65933e-04
seoc7498	1R	0.04	fcrc5160	1V	3.03966e-04
seob3485	1R	0.04	mioa3940	1V	3.03966e-04
ncrb8468	1R	0.04	seob7765	1V	3.03966e-04
fcrb6005	1R	0.04	fcr3575	1V	3.19001e-04
ncrb8539	1R	0.04	miod5030	1V	3.46873e-04
ncrc5016	1R	0.04	fcrb3544	1V	3.47e-04
ncr2288	1R	0.04	seoc1235	1V	3.49e-04
fcrb1920	1R	0.04	seoa5156	1V	3.5e-04
fcrb8020	1R	0.04	ncrb0164	1V	3.54e-04
seoa4132	1R	0.04	ncrc5025	1V	3.55e-04
seoa9870	1R	0.04	seoa6661	1V	3.66e-04
seob0876	1R	0.04	ncrc4985	1V	3.68e-04
seob2990	1R	0.04	seob7622	1V	3.68e-04

fcr2860	1V	3.7e-04	fcrc7219	1V	5.78978e-04
fcr4128	1V	3.7e-04	mioc2872	1V	5.78978e-04
fcrb1539	1V	3.7e-04	ncrc2857	1V	5.78978e-04
fcrb1990	1V	3.7e-04	seob9851	1V	5.78978e-04
fcrb2330	1V	3.7e-04	mioa8380	1V	5.8e-04
fcrb3119	1V	3.7e-04	hfcr0229	1V	6.04e-04
fcrb5269	1V	3.7e-04	fcrb5351	1V	6.14e-04
fcrb5536	1V	3.7e-04	seob9614	1V	6.2227e-04
fcrb5564	1V	3.7e-04	fcrb5896	1V	6.33e-04
fcrb6251	1V	3.7e-04	fcrc2724	1V	6.33e-04
fcrb6596	1V	3.7e-04	mioc7370	1V	6.33e-04
fcrb6639	1V	3.7e-04	fcr2299	1V	6.35519e-04
fcrb7084	1V	3.7e-04	fcr3053	1V	6.55553e-04
fcrb7693	1V	3.7e-04	fcrc5137	1V	6.55553e-04
fcrc2745	1V	3.7e-04	fcrc5614	1V	6.55553e-04
fcrc2849	1V	3.7e-04	mioa3668	1V	6.55553e-04
fcrc5480	1V	3.7e-04	mioc4493	1V	6.55553e-04
miob1561	1V	3.7e-04	seoa5898	1V	6.55553e-04
miob3456	1V	3.7e-04	seoa8993	1V	6.55553e-04
miob8816	1V	3.7e-04	seoa9160	1V	6.55553e-04
miob9248	1V	3.7e-04	seob2987	1V	6.55553e-04
miob9393	1V	3.7e-04	ncrc3460	1V	7.23e-04
mioc4022	1V	3.7e-04	seob3088	1V	7.31e-04
mioc5622	1V	3.7e-04	fcrb9611	1V	7.41141e-04
ncr1545	1V	3.7e-04	fcrc5107	1V	7.41141e-04
ncrb2288	1V	3.7e-04	mioc3682	1V	7.41141e-04
ncrb7482	1V	3.7e-04	ncrb0749	1V	7.41141e-04
ncrc2443	1V	3.7e-04	seoc3690	1V	7.41141e-04
ncrc5363	1V	3.7e-04	seoc1642	1V	7.46e-04
seoa2209	1V	3.7e-04	fcrb8340	1V	7.85e-04
seoa3230	1V	3.7e-04	miob8825	1V	7.85e-04
seoa7340	1V	3.7e-04	seob9869	1V	8.13e-04
seoa8997	1V	3.7e-04	mioc4161	1V	8.18e-04
seob0303	1V	3.7e-04	fcrb8668	1V	8.3666e-04
seob0763	1V	3.7e-04	fcrc5041	1V	8.3666e-04
seob0872	1V	3.7e-04	fcrc5086	1V	8.3666e-04
seob1426	1V	3.7e-04	fcrc6932	1V	8.3666e-04
seoc1661	1V	3.7e-04	hfcr3058	1V	8.3666e-04
seoc2221	1V	3.7e-04	seob6437	1V	8.3666e-04
mioa4753	1V	3.89e-04	seob9772	1V	8.3666e-04
fcrb8114	1V	3.91e-04	seoa1318	1V	8.39e-04
seoa1749	1V	3.95201e-04	fcrb9420	1V	8.44e-04
miob9124	1V	4.2e-04	fcrb6715	1V	8.66e-04
fcrc0430	1V	4.28e-04	ncr2575	1V	9.04e-04
seoa5977	1V	4.43e-04	ncrc4875	1V	9.26e-04
fcrl1772	1V	4.49e-04	miob9285	1V	9.36e-04
fcrc5577	1V	4.49548e-04	fcrb1684	1V	9.43108e-04
miob7794	1V	4.49548e-04	fcrb2113	1V	9.43108e-04
ncr4030	1V	4.49548e-04	fcrb3686	1V	9.43108e-04
ncrc0576	1V	4.49548e-04	mioa8864	1V	9.43108e-04
seoa0429	1V	4.68e-04	miob3695	1V	9.43108e-04
fcrb3680	1V	4.71e-04	miob4574	1V	9.43108e-04
ncr0133	1V	4.83e-04	miob8609	1V	9.43108e-04
fcrb6785	1V	5.10569e-04	seoa0799	1V	9.43108e-04
miob0764	1V	5.10569e-04	seob6379	1V	9.43108e-04
mioc3827	1V	5.10569e-04	seoc4380	1V	9.43108e-04
ncrb0046	1V	5.10569e-04	seob6380	1V	9.5e-04
seob1362	1V	5.10569e-04	seob2994	1V	9.76e-04
seoc0149	1V	5.10569e-04	ncrc5039	1V	9.97e-04
fcrc4180	1V	5.27e-04	mioc1354	1V	1.061561e-03
fcrb3763	1V	5.67e-04	ncrb1167	1V	1.073748e-03
ncrc3283	1V	5.67e-04	seoa3895	1V	1.119756e-03
ncrc3358	1V	5.67e-04	seoc1307	1V	1.151704e-03
fcr4328	1V	5.78978e-04	seoa1737	1V	1.155164e-03

ncrc9899	1V	1.170347e-03	ncrc3598	1V	1.476515e-03
fcrb3734	1V	1.170828e-03	ncrc4076	1V	1.476515e-03
seob0133	1V	1.181737e-03	ncrc5688	1V	1.476515e-03
miob3618	1V	1.193188e-03	ncrc8988	1V	1.476515e-03
miob7106	1V	1.193188e-03	seoa1856	1V	1.476515e-03
miob7638	1V	1.193188e-03	seoa2768	1V	1.476515e-03
ncrb0328	1V	1.193188e-03	seoa3891	1V	1.476515e-03
ncrc0461	1V	1.193188e-03	seoa4681	1V	1.476515e-03
seob4555	1V	1.193188e-03	seoa5235	1V	1.476515e-03
seoc0034	1V	1.193188e-03	seoa6557	1V	1.476515e-03
mioa0192	1V	1.218739e-03	seoa7517	1V	1.476515e-03
miod4735	1V	1.252641e-03	seoa7530	1V	1.476515e-03
mioa1906	1V	1.255827e-03	seoa8424	1V	1.476515e-03
mioa8973	1V	1.256375e-03	seoa9627	1V	1.476515e-03
seoa9724	1V	1.27253e-03	seoa9792	1V	1.476515e-03
miod1316	1V	1.29623e-03	seob0370	1V	1.476515e-03
ncrc9159	1V	1.326356e-03	seob1947	1V	1.476515e-03
fcr3001	1V	1.339245e-03	seob5556	1V	1.476515e-03
fcrb8908	1V	1.339245e-03	seoc2722	1V	1.476515e-03
fcrc0591	1V	1.339245e-03	mioa8987	1V	1.493237e-03
fcrc2775	1V	1.339245e-03	miob7319	1V	1.494352e-03
fcrc7056	1V	1.339245e-03	mioa0311	1V	1.501088e-03
hfcr2629	1V	1.339245e-03	mioa2173	1V	1.501088e-03
miob2836	1V	1.339245e-03	ncr4135	1V	1.501088e-03
mioc0669	1V	1.339245e-03	ncrb2544	1V	1.501088e-03
miod3946	1V	1.339245e-03	ncrb4166	1V	1.501088e-03
ncrc0964	1V	1.339245e-03	seoa0536	1V	1.501088e-03
ncrc9052	1V	1.339245e-03	seob8562	1V	1.501088e-03
seoa6172	1V	1.339245e-03	hfcr2670	1V	1.548822e-03
seob4734	1V	1.339245e-03	seoa5554	1V	1.560016e-03
seob7424	1V	1.339245e-03	miob9748	1V	1.637446e-03
fcr4380	1V	1.411242e-03	hfcr0263	1V	1.680177e-03
miod3914	1V	1.413142e-03	hfcr5991	1V	1.680177e-03
miod7081	1V	1.426601e-03	hfcr6613	1V	1.680177e-03
miod1323	1V	1.440791e-03	mioa3913	1V	1.680177e-03
fcrb1922	1V	1.458522e-03	ncrb3768	1V	1.680177e-03
ncr4189	1V	1.458522e-03	fcr0748	1V	1.690349e-03
fcr1756	1V	1.476515e-03	fcrb2292	1V	1.706646e-03
fcr4494	1V	1.476515e-03	fcrc6990	1V	1.722062e-03
fcr4902	1V	1.476515e-03	seob3226	1V	1.79599e-03
fcrb1575	1V	1.476515e-03	seob2728	1V	1.80089e-03
fcrb2483	1V	1.476515e-03	hfcr3444	1V	1.835381e-03
fcrb4470	1V	1.476515e-03	fcr2102	1V	1.844189e-03
fcrb4717	1V	1.476515e-03	fcr3856	1V	1.878078e-03
fcrb7036	1V	1.476515e-03	mioa8952	1V	1.878078e-03
fcrb9454	1V	1.476515e-03	miob8487	1V	1.878078e-03
fcrc0529	1V	1.476515e-03	miod5060	1V	1.878078e-03
fcrc5471	1V	1.476515e-03	miod5123	1V	1.878078e-03
fcrc7222	1V	1.476515e-03	ncr6344	1V	1.878078e-03
hfcr3647	1V	1.476515e-03	seoa0501	1V	1.878078e-03
mioa1626	1V	1.476515e-03	seoa8239	1V	1.878078e-03
miob3307	1V	1.476515e-03	seoc5228	1V	1.878078e-03
miob9734	1V	1.476515e-03	fcrb2800	1V	1.898609e-03
miob9788	1V	1.476515e-03	ncr0634	1V	1.92683e-03
mioc0911	1V	1.476515e-03	seoa4795	1V	1.961962e-03
mioc7364	1V	1.476515e-03	seob7906	1V	1.97218e-03
miod1448	1V	1.476515e-03	fcrc5482	1V	2.019211e-03
miod5092	1V	1.476515e-03	ncrc5230	1V	2.026769e-03
miod7212	1V	1.476515e-03	seoa2805	1V	2.092754e-03
ncr0025	1V	1.476515e-03	fcr2276	1V	2.096472e-03
ncr2967	1V	1.476515e-03	fcrb4345	1V	2.096472e-03
ncr8538	1V	1.476515e-03	fcrc1563	1V	2.096472e-03
ncrb3638	1V	1.476515e-03	fcrc5290	1V	2.096472e-03
ncrc1780	1V	1.476515e-03	fcrc6002	1V	2.096472e-03

mioa0597	1V	2.096472e-03	ncr1712	1V	2.893252e-03
miob7662	1V	2.096472e-03	ncrc2161	1V	2.893252e-03
miob8320	1V	2.096472e-03	seoa2391	1V	2.893252e-03
miod5010	1V	2.096472e-03	seob4145	1V	2.893252e-03
miod5256	1V	2.096472e-03	seob9543	1V	2.893252e-03
ncr3825	1V	2.096472e-03	ncr0491	1V	2.89732e-03
ncrb6109	1V	2.096472e-03	seoc1628	1V	3.049387e-03
seoa0207	1V	2.096472e-03	seob6156	1V	3.053926e-03
ncrb2092	1V	2.134438e-03	ncrc4033	1V	3.104345e-03
fcrb1992	1V	2.209983e-03	seob8287	1V	3.182459e-03
seoa3761	1V	2.225021e-03	mioc0302	1V	3.183214e-03
miod4407	1V	2.228163e-03	mioc0621	1V	3.183214e-03
seoa5433	1V	2.23127e-03	ncr2930	1V	3.183214e-03
seoa6620	1V	2.299089e-03	mioc3369	1V	3.203555e-03
fcrb3615	1V	2.337161e-03	ncrc9877	1V	3.209695e-03
fcrb3870	1V	2.337161e-03	fcr1555	1V	3.212904e-03
fcrb5296	1V	2.337161e-03	fcr4129	1V	3.212904e-03
fcrb6508	1V	2.337161e-03	fcrb5467	1V	3.212904e-03
fcrb8119	1V	2.337161e-03	fcrb8236	1V	3.212904e-03
fcrb8215	1V	2.337161e-03	mioa7617	1V	3.212904e-03
fcrc5139	1V	2.337161e-03	mioc4269	1V	3.212904e-03
mioc5198	1V	2.337161e-03	ncr4656	1V	3.212904e-03
mioc6560	1V	2.337161e-03	ncr7923	1V	3.212904e-03
ncr3782	1V	2.337161e-03	ncr8153	1V	3.212904e-03
ncrb0027	1V	2.337161e-03	seoa1599	1V	3.212904e-03
ncrb4477	1V	2.337161e-03	seoa8912	1V	3.212904e-03
ncrb7166	1V	2.337161e-03	mioc1060	1V	3.280556e-03
seoa1173	1V	2.337161e-03	ncrc2675	1V	3.327646e-03
seob1808	1V	2.337161e-03	ncr8725	1V	3.386385e-03
seob6206	1V	2.342651e-03	fcrb2713	1V	3.387122e-03
miob9087	1V	2.3779e-03	fcrb6031	1V	3.409264e-03
seob0321	1V	2.379735e-03	hfcr2536	1V	3.539273e-03
miob3594	1V	2.406345e-03	mioa9491	1V	3.55572e-03
fcrb4067	1V	2.48884e-03	fcr2940	1V	3.558947e-03
seob0937	1V	2.540573e-03	fcr5536	1V	3.563359e-03
mioc3220	1V	2.541667e-03	fcrb1731	1V	3.563359e-03
fcrb9684	1V	2.564635e-03	mioc2166	1V	3.563359e-03
seob7575	1V	2.564635e-03	ncrb0045	1V	3.563359e-03
fcr0061	1V	2.602068e-03	ncrb0074	1V	3.563359e-03
fcr3282	1V	2.602068e-03	ncrb2517	1V	3.563359e-03
fcrc0379	1V	2.602068e-03	ncrc6846	1V	3.563359e-03
fcrc4390	1V	2.602068e-03	seoa1992	1V	3.563359e-03
miob5940	1V	2.602068e-03	seoa6152	1V	3.563359e-03
mioc3603	1V	2.602068e-03	seoa8177	1V	3.563359e-03
mioc1377	1V	2.602068e-03	seob0058	1V	3.563359e-03
mioc5771	1V	2.602068e-03	seob6133	1V	3.563359e-03
mioc6324	1V	2.602068e-03	seoc0951	1V	3.563359e-03
ncrc8863	1V	2.602068e-03	seoc3659	1V	3.563359e-03
seoa1598	1V	2.602068e-03	seoc4928	1V	3.563359e-03
seob4303	1V	2.602068e-03	ncr4454	1V	3.575847e-03
fcrb6929	1V	2.604001e-03	seob3882	1V	3.664302e-03
ncrc2959	1V	2.604001e-03	seob0085	1V	3.701885e-03
fcrb1337	1V	2.697142e-03	mioa6726	1V	3.711483e-03
fcrc5690	1V	2.697142e-03	ncrb8646	1V	3.711654e-03
ncr0165	1V	2.697142e-03	seoa3717	1V	3.749508e-03
seoa6131	1V	2.721704e-03	seoa8399	1V	3.841578e-03
fcr4503	1V	2.721914e-03	fcrb5375	1V	3.881761e-03
mioc4857	1V	2.870616e-03	miob9533	1V	3.895277e-03
fcr1328	1V	2.893252e-03	ncrb6742	1V	3.895528e-03
fcrc2573	1V	2.893252e-03	seoc5006	1V	3.929979e-03
fcrc5671	1V	2.893252e-03	fcrb1876	1V	3.9471e-03
hfcr5611	1V	2.893252e-03	fcrc2954	1V	3.9471e-03
mioc3669	1V	2.893252e-03	mioa2204	1V	3.9471e-03
mioc0080	1V	2.893252e-03	mioa8970	1V	3.9471e-03

mioa9604	1V	3.9471e-03	ncrc2831	1V	4.204851e-03
miob8691	1V	3.9471e-03	ncrc2919	1V	4.204851e-03
mioc7201	1V	3.9471e-03	ncrc4907	1V	4.204851e-03
miod5310	1V	3.9471e-03	ncrc5312	1V	4.204851e-03
miod6845	1V	3.9471e-03	ncrc8841	1V	4.204851e-03
ncr8481	1V	3.9471e-03	ncrc8949	1V	4.204851e-03
ncrb8239	1V	3.9471e-03	ncrc9328	1V	4.204851e-03
ncrc3855	1V	3.9471e-03	ncrc9910	1V	4.204851e-03
ncrc5376	1V	3.9471e-03	seoa0388	1V	4.204851e-03
ncrc6587	1V	3.9471e-03	seoa3147	1V	4.204851e-03
seoa0256	1V	3.9471e-03	seoa6137	1V	4.204851e-03
seob7278	1V	3.9471e-03	seoa6393	1V	4.204851e-03
miob8754	1V	3.989036e-03	seoa6497	1V	4.204851e-03
seob7584	1V	4.012618e-03	seoa6598	1V	4.204851e-03
ncrb8171	1V	4.135195e-03	seoa6718	1V	4.204851e-03
mioc1416	1V	4.135238e-03	seoa7157	1V	4.204851e-03
seob0046	1V	4.135238e-03	seoa8543	1V	4.204851e-03
miob9209	1V	4.157852e-03	seoa9302	1V	4.204851e-03
fcrb2308	1V	4.204851e-03	seob0034	1V	4.204851e-03
fcrb3181	1V	4.204851e-03	seob0154	1V	4.204851e-03
fcrb3201	1V	4.204851e-03	seob0426	1V	4.204851e-03
fcrb4241	1V	4.204851e-03	seob1081	1V	4.204851e-03
fcrb4270	1V	4.204851e-03	seob4645	1V	4.204851e-03
fcrb4294	1V	4.204851e-03	seob5319	1V	4.204851e-03
fcrb4360	1V	4.204851e-03	seob5743	1V	4.204851e-03
fcrb4417	1V	4.204851e-03	seob5748	1V	4.204851e-03
fcrb4963	1V	4.204851e-03	seob5899	1V	4.204851e-03
fcrb5688	1V	4.204851e-03	seob7474	1V	4.204851e-03
fcrb8449	1V	4.204851e-03	seob8483	1V	4.204851e-03
fcrb9371	1V	4.204851e-03	seoc0843	1V	4.204851e-03
fcrc1758	1V	4.204851e-03	fcr0903	1V	4.316218e-03
fcrc2306	1V	4.204851e-03	fcr1499	1V	4.339479e-03
fcrc5583	1V	4.204851e-03	hfcrc3143	1V	4.349057e-03
hfcrc3022	1V	4.204851e-03	mioc3139	1V	4.358139e-03
mioa1520	1V	4.204851e-03	fcrb3627	1V	4.366761e-03
mioa3321	1V	4.204851e-03	fcrb5503	1V	4.366761e-03
mioa3673	1V	4.204851e-03	fcrc1402	1V	4.366761e-03
mioa4076	1V	4.204851e-03	fcrc5771	1V	4.366761e-03
mioa4564	1V	4.204851e-03	hfcrc2895	1V	4.366761e-03
mioa5085	1V	4.204851e-03	miob2668	1V	4.366761e-03
mioa5692	1V	4.204851e-03	miod5672	1V	4.366761e-03
mioa5955	1V	4.204851e-03	ncr4416	1V	4.366761e-03
miob3953	1V	4.204851e-03	ncrb0696	1V	4.366761e-03
mioc1229	1V	4.204851e-03	ncrb8585	1V	4.366761e-03
mioc2209	1V	4.204851e-03	seoa1616	1V	4.366761e-03
mioc2348	1V	4.204851e-03	seob4293	1V	4.366761e-03
mioc2451	1V	4.204851e-03	seoc0284	1V	4.366761e-03
mioc2577	1V	4.204851e-03	seoc0742	1V	4.366761e-03
mioc4112	1V	4.204851e-03	seoc4381	1V	4.366761e-03
mioc6374	1V	4.204851e-03	fcrc5007	1V	4.388153e-03
miod2128	1V	4.204851e-03	seob0185	1V	4.388153e-03
miod3160	1V	4.204851e-03	miod7414	1V	4.474241e-03
miod6048	1V	4.204851e-03	seoc2549	1V	4.489551e-03
miod6521	1V	4.204851e-03	mioc4351	1V	4.538604e-03
miod7324	1V	4.204851e-03	mioc8481	1V	4.678627e-03
ncr0638	1V	4.204851e-03	miod4686	1V	4.740394e-03
ncr1305	1V	4.204851e-03	fcr2972	1V	4.825136e-03
ncr1550	1V	4.204851e-03	fcrc4551	1V	4.825136e-03
ncrb0207	1V	4.204851e-03	fcrc6174	1V	4.825136e-03
ncrb3348	1V	4.204851e-03	hfcrc4497	1V	4.825136e-03
ncrb8538	1V	4.204851e-03	miob2285	1V	4.825136e-03
ncrc0539	1V	4.204851e-03	mioc1600	1V	4.825136e-03
ncrc1247	1V	4.204851e-03	miod4932	1V	4.825136e-03
ncrc1595	1V	4.204851e-03	ncr8096	1V	4.825136e-03

ncrc9784	1V	4.825136e-03	fcr2935	1V	5.990508e-03
seoa4107	1V	4.825136e-03	seob6851	1V	6.032512e-03
seob4105	1V	4.825136e-03	seob7309	1V	6.107204e-03
seob7866	1V	4.825136e-03	fcrb7760	1V	6.130086e-03
seoa2899	1V	4.826733e-03	ncrc5088	1V	6.197231e-03
hfc0489	1V	4.869783e-03	seob2661	1V	6.211987e-03
fcrb5527	1V	4.888032e-03	mioc2021	1V	6.236422e-03
seob5551	1V	4.908034e-03	seoc1804	1V	6.261128e-03
mioa4077	1V	4.909178e-03	miob8463	1V	6.391219e-03
ncrc9228	1V	4.93663e-03	fcrc0959	1V	6.416508e-03
fcrb3120	1V	5.081016e-03	ncr2484	1V	6.42957e-03
ncrc4448	1V	5.161235e-03	fcrb6301	1V	6.441057e-03
hfc05865	1V	5.255535e-03	fcr1347	1V	6.462965e-03
fcrb3715	1V	5.312325e-03	fcrb5241	1V	6.462965e-03
fcrb7852	1V	5.318621e-03	fcrc5391	1V	6.462965e-03
ncrb7027	1V	5.324125e-03	mioa0497	1V	6.462965e-03
fcr1312	1V	5.325183e-03	miob3531	1V	6.462965e-03
fcrb8542	1V	5.325183e-03	miob6713	1V	6.462965e-03
fcrc6465	1V	5.325183e-03	miod0456	1V	6.462965e-03
fcrc7046	1V	5.325183e-03	ncr2869	1V	6.462965e-03
mioa1473	1V	5.325183e-03	ncr7668	1V	6.462965e-03
mioa9891	1V	5.325183e-03	ncrc0249	1V	6.462965e-03
miob0167	1V	5.325183e-03	ncrc3596	1V	6.462965e-03
miob3247	1V	5.325183e-03	ncrc4654	1V	6.462965e-03
miob5751	1V	5.325183e-03	ncrc6417	1V	6.462965e-03
miod5258	1V	5.325183e-03	seoa1747	1V	6.462965e-03
ncrc6588	1V	5.325183e-03	seoa2822	1V	6.462965e-03
seoa4647	1V	5.325183e-03	seoa6754	1V	6.462965e-03
seob3064	1V	5.325183e-03	seoa9363	1V	6.462965e-03
seob6096	1V	5.325183e-03	seob0201	1V	6.462965e-03
seoc0369	1V	5.325183e-03	seob3170	1V	6.462965e-03
miob9163	1V	5.338918e-03	seob7729	1V	6.462965e-03
seoa6930	1V	5.338918e-03	seob9756	1V	6.462965e-03
seob2685	1V	5.358138e-03	ncrb7350	1V	6.507615e-03
miob0974	1V	5.376436e-03	seob9970	1V	6.507615e-03
fcrb6107	1V	5.429727e-03	seoa8300	1V	6.520751e-03
seob4689	1V	5.482935e-03	fcrc4663	1V	6.53971e-03
hfc02686	1V	5.502936e-03	hfc03404	1V	6.5438e-03
seoa9712	1V	5.541398e-03	fcrb6363	1V	6.573178e-03
mioc2403	1V	5.546828e-03	seob5889	1V	6.584665e-03
mioc2592	1V	5.591403e-03	fcrb1767	1V	6.5959e-03
seoa4066	1V	5.634661e-03	miob7109	1V	6.695564e-03
miob8274	1V	5.669235e-03	mioc2961	1V	6.726375e-03
mioa5558	1V	5.842704e-03	ncrc3690	1V	6.760566e-03
ncr3614	1V	5.868299e-03	seob6272	1V	6.914972e-03
fcr6748	1V	5.870026e-03	fcrb6776	1V	6.94408e-03
fcrb5449	1V	5.870026e-03	ncrb8802	1V	6.973937e-03
fcrc0180	1V	5.870026e-03	fcr5257	1V	7.107476e-03
mioa2038	1V	5.870026e-03	fcrb6279	1V	7.107476e-03
mioa6556	1V	5.870026e-03	fcrb7812	1V	7.107476e-03
miob2227	1V	5.870026e-03	mioa9246	1V	7.107476e-03
miob9678	1V	5.870026e-03	miob1814	1V	7.107476e-03
mioc5182	1V	5.870026e-03	miob4803	1V	7.107476e-03
miod4019	1V	5.870026e-03	miob6632	1V	7.107476e-03
ncr8111	1V	5.870026e-03	mioc0899	1V	7.107476e-03
ncrb0220	1V	5.870026e-03	mioc2619	1V	7.107476e-03
seoa1834	1V	5.870026e-03	ncr1299	1V	7.107476e-03
seoa4264	1V	5.870026e-03	ncr4612	1V	7.107476e-03
seoa5138	1V	5.870026e-03	ncr7904	1V	7.107476e-03
seoc1764	1V	5.870026e-03	ncrb3424	1V	7.107476e-03
seoc3374	1V	5.870026e-03	ncrc2796	1V	7.107476e-03
fcrb5254	1V	5.873716e-03	ncrc3551	1V	7.107476e-03
hfc03844	1V	5.898035e-03	ncrc4798	1V	7.107476e-03
fcr0999	1V	5.963463e-03	ncrc9044	1V	7.107476e-03

ncrc9525	1V	7.107476e-03	mioa2374	1V	8.566036e-03
seoa1736	1V	7.107476e-03	mioa3486	1V	8.566036e-03
seoa1802	1V	7.107476e-03	mioa4037	1V	8.566036e-03
seoa9373	1V	7.107476e-03	mioa4177	1V	8.566036e-03
seob2953	1V	7.107476e-03	ncr3112	1V	8.566036e-03
seob7039	1V	7.107476e-03	ncr7382	1V	8.566036e-03
ncrc9483	1V	7.135877e-03	ncrb6903	1V	8.566036e-03
fcrb1867	1V	7.149399e-03	seoa4524	1V	8.566036e-03
fcrb6351	1V	7.150346e-03	seoc0317	1V	8.566036e-03
fcrc5024	1V	7.17138e-03	miob8707	1V	8.631338e-03
hfcr3436	1V	7.17138e-03	fcrc6228	1V	8.668265e-03
ncr3442	1V	7.17138e-03	fcrb2166	1V	8.677358e-03
ncrb0653	1V	7.17138e-03	fcrb8852	1V	8.677358e-03
ncrb6327	1V	7.17138e-03	fcrc6916	1V	8.677358e-03
fcrc4150	1V	7.20619e-03	seoa4608	1V	8.697131e-03
seoa0792	1V	7.296919e-03	seob6279	1V	8.785727e-03
fcrb5438	1V	7.315319e-03	ncrc9259	1V	8.793602e-03
ncr2861	1V	7.37339e-03	seob0084	1V	8.825601e-03
seoc4824	1V	7.406399e-03	fcr4224	1V	8.856803e-03
ncrc6825	1V	7.490077e-03	fcrb7785	1V	8.880688e-03
seob5684	1V	7.493924e-03	seoc8115	1V	9.082651e-03
fcrb2424	1V	7.538874e-03	mioa4738	1V	9.101947e-03
hfcr5942	1V	7.555731e-03	seoa7546	1V	9.109835e-03
miob4370	1V	7.592592e-03	miob3174	1V	9.150755e-03
seoa0221	1V	7.677171e-03	fcrb8161	1V	9.192222e-03
seoc2050	1V	7.769248e-03	seob5044	1V	9.283845e-03
fcr3861	1V	7.78102e-03	hfcr2389	1V	9.342306e-03
fcr5728	1V	7.78102e-03	fcrb2818	1V	9.351412e-03
mioc2950	1V	7.78102e-03	fcrb5918	1V	9.360485e-03
ncrc3856	1V	7.78102e-03	fcrc6016	1V	9.367048e-03
ncrc6459	1V	7.78102e-03	ncrc5146	1V	9.367346e-03
fcrb2749	1V	7.807218e-03	fcr4803	1V	9.387964e-03
fcrb5272	1V	7.807218e-03	fcr5316	1V	9.387964e-03
fcrb5389	1V	7.807218e-03	fcrb4789	1V	9.387964e-03
fcrb6549	1V	7.807218e-03	fcrb9499	1V	9.387964e-03
hfcr3518	1V	7.807218e-03	fcrc2536	1V	9.387964e-03
mioa9492	1V	7.807218e-03	fcrc5142	1V	9.387964e-03
miob3308	1V	7.807218e-03	fcrc5506	1V	9.387964e-03
mioc6134	1V	7.807218e-03	fcrc7180	1V	9.387964e-03
ncrb0054	1V	7.807218e-03	hfcr5919	1V	9.387964e-03
ncrc5316	1V	7.807218e-03	miob2705	1V	9.387964e-03
ncrc6597	1V	7.807218e-03	miob4144	1V	9.387964e-03
ncrc7023	1V	7.807218e-03	mioc2110	1V	9.387964e-03
ncrc9795	1V	7.807218e-03	mioc6156	1V	9.387964e-03
seob7941	1V	7.807218e-03	mioc4629	1V	9.387964e-03
seob9627	1V	7.807218e-03	mioc6961	1V	9.387964e-03
ncrc6264	1V	7.987052e-03	ncr0159	1V	9.387964e-03
seoa9740	1V	7.991283e-03	ncr1523	1V	9.387964e-03
seob3326	1V	8.004907e-03	ncr4654	1V	9.387964e-03
fcrb8121	1V	8.06206e-03	ncr5065	1V	9.387964e-03
fcrb5929	1V	8.173274e-03	ncrb2085	1V	9.387964e-03
seoa7178	1V	8.208048e-03	ncrc6778	1V	9.387964e-03
miob6087	1V	8.227431e-03	seoa6658	1V	9.387964e-03
mioc0981	1V	8.229427e-03	seob1187	1V	9.387964e-03
ncrc5760	1V	8.24867e-03	seob3303	1V	9.387964e-03
mioa3084	1V	8.251328e-03	seoc1948	1V	9.387964e-03
seob5903	1V	8.35087e-03	seob0089	1V	9.434517e-03
fcrb1399	1V	8.385639e-03	ncr4550	1V	9.487359e-03
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fcr3033	1V	8.446509e-03	mioc0530	1V	9.561475e-03
seoa2978	1V	8.471198e-03	ncrb8396	1V	9.591184e-03
ncr3965	1V	8.490122e-03	fcr0511	1V	9.682221e-03
fcrb4589	1V	8.566036e-03	fcr0837	1V	9.682221e-03
fcrb8504	1V	8.566036e-03	fcr1337	1V	9.682221e-03



fcr3559	1V	9.682221e-03	seob1842	1V	9.682221e-03
fcrb1729	1V	9.682221e-03	seob1898	1V	9.682221e-03
fcrb2203	1V	9.682221e-03	seob5773	1V	9.682221e-03
fcrb3024	1V	9.682221e-03	seob6560	1V	9.682221e-03
fcrb3857	1V	9.682221e-03	seoc0355	1V	9.682221e-03
fcrb3874	1V	9.682221e-03	seoc3870	1V	9.682221e-03
fcrb5537	1V	9.682221e-03	seoc4960	1V	9.682221e-03
fcrb5709	1V	9.682221e-03	seoc6703	1V	9.682221e-03
fcrb5912	1V	9.682221e-03	ncrb4248	1V	9.724687e-03
fcrb6874	1V	9.682221e-03	fcrc6877	1V	9.907979e-03
fcrb9914	1V	9.682221e-03	mioa4667	1V	0.01
fcrc1085	1V	9.682221e-03	mioc7331	1V	0.01
fcrc4722	1V	9.682221e-03	hfcr5959	1V	0.01
fcrc6452	1V	9.682221e-03	seob1862	1V	0.01
hfcr0045	1V	9.682221e-03	fcr2220	1V	0.01
hfcr5003	1V	9.682221e-03	fcrc2231	1V	0.01
mioa2413	1V	9.682221e-03	fcrc6855	1V	0.01
mioa2447	1V	9.682221e-03	fcrc6898	1V	0.01
mioa4326	1V	9.682221e-03	miob2869	1V	0.01
mioa4818	1V	9.682221e-03	miob4037	1V	0.01
miob0681	1V	9.682221e-03	miod1236	1V	0.01
miob1830	1V	9.682221e-03	ncr9324	1V	0.01
miob2686	1V	9.682221e-03	ncr9502	1V	0.01
miob3461	1V	9.682221e-03	ncrc4219	1V	0.01
miob3937	1V	9.682221e-03	ncrc4757	1V	0.01
miob4055	1V	9.682221e-03	ncrc6920	1V	0.01
miob4735	1V	9.682221e-03	ncrc9519	1V	0.01
miob6442	1V	9.682221e-03	seoa0186	1V	0.01
miob6615	1V	9.682221e-03	seoa1552	1V	0.01
miob8572	1V	9.682221e-03	seob1420	1V	0.01
miob8694	1V	9.682221e-03	seob1906	1V	0.01
mioc1086	1V	9.682221e-03	seoc0698	1V	0.01
mioc2541	1V	9.682221e-03	seoc4410	1V	0.01
mioc3206	1V	9.682221e-03	miob0207	1V	0.01
mioc4318	1V	9.682221e-03	miob8616	1V	0.01
miod4752	1V	9.682221e-03	mioc9881	1V	0.01
ncr2926	1V	9.682221e-03	miob2287	1V	0.01
ncr3690	1V	9.682221e-03	miod6437	1V	0.01
ncr3815	1V	9.682221e-03	seob5465	1V	0.01
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ncr8693	1V	9.682221e-03	hfcr2756	1V	0.01
ncrb0145	1V	9.682221e-03	seoa1615	1V	0.01
ncrb6762	1V	9.682221e-03	mioc2385	1V	0.01
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ncrc0744	1V	9.682221e-03	mioc1991	1V	0.01
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ncrc4940	1V	9.682221e-03	fcrb4378	1V	0.01
ncrc5016	1V	9.682221e-03	fcr0107	1V	0.01
ncrc5072	1V	9.682221e-03	fcr1060	1V	0.01
ncrc6371	1V	9.682221e-03	fcrb1369	1V	0.01
ncrc8963	1V	9.682221e-03	fcrb1492	1V	0.01
seoa1770	1V	9.682221e-03	fcrb6718	1V	0.01
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seoa3108	1V	9.682221e-03	mioa0245	1V	0.01
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seoa6315	1V	9.682221e-03	mioa8796	1V	0.01
seoa8638	1V	9.682221e-03	miob7945	1V	0.01
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seob0308	1V	9.682221e-03	miob8947	1V	0.01
seob0975	1V	9.682221e-03	mioc2216	1V	0.01
seob1323	1V	9.682221e-03	miod1291	1V	0.01
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fcrb4616	1V	0.01
fcrb5756	1V	0.01
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mioa1343	1V	0.01
mioa2292	1V	0.01
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fcrb3079	1V	0.01
seoc1203	1V	0.01
ncrc9237	1V	0.01
fcrb9636	1V	0.01
miob4570	1V	0.01
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hfcr3144	1V	0.01
fcrb2299	1V	0.01
seob9145	1V	0.01
ncr4126	1V	0.01
fcrb5007	1V	0.01
seob6026	1V	0.01
fcrb4734	1V	0.01
miod0625	1V	0.01
seob6835	1V	0.01
ncr9175	1V	0.01
fcr0824	1V	0.01
ncrc9704	1V	0.01
mioa4810	1V	0.01
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fcr0707	1V	0.01
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fcrb6438	1V	0.01
fcrb7602	1V	0.01
fcrb8208	1V	0.01
fcrc2884	1V	0.01
hfcrc2850	1V	0.01
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mioa6093	1V	0.01
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mioc0090	1V	0.01
mioc0528	1V	0.01
mioc3958	1V	0.01
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miod6644	1V	0.01
miod6671	1V	0.01
miod7225	1V	0.01
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seoa1979	1V	0.01
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seoa9873	1V	0.01
seob2642	1V	0.01
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fcrb9017	1V	0.01
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miob3358	1V	0.01
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fcrc2705	1V	0.01
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miob1811	1V	0.01
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miod1056	1V	0.01
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seoa1720	1V	0.01
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fcrc6397	1V	0.01
mioa4606	1V	0.01
fcr6708	1V	0.01
seob3139	1V	0.01
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fcrb2804	1V	0.01
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seob6041	1V	0.01
seob8257	1V	0.01
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fcrc6976	1V	0.01
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miob2687	1V	0.01
miob2941	1V	0.01
miob4368	1V	0.01
miob9128	1V	0.01
miod1157	1V	0.01
miod6488	1V	0.01
ncr0547	1V	0.01
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ncr3163	1V	0.01
ncr6415	1V	0.01
ncr8866	1V	0.01
ncrb0364	1V	0.01
ncrc3593	1V	0.01
seoa4829	1V	0.01
seoa5986	1V	0.01
seoa7373	1V	0.01
seob1197	1V	0.01
seob4075	1V	0.01
seob4117	1V	0.01
seob4270	1V	0.01
seob9282	1V	0.01
seoc1856	1V	0.01
seoc4038	1V	0.01
fcrb4271	1V	0.01
seoa9729	1V	0.01
seoa5552	1V	0.01
fcrc6833	1V	0.01

ncr5651	1V	0.01
fcrc2429	1V	0.01
ncrc7085	1V	0.01
mioa3963	1V	0.01
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mioc0206	1V	0.01
ncr5709	1V	0.01
seoa5787	1V	0.01
seob6492	1V	0.01
seob8194	1V	0.01
fcr2908	1V	0.01
fcrb6181	1V	0.01
seoa2141	1V	0.01
seoa5578	1V	0.01
seoa4158	1V	0.01
seoc3277	1V	0.01
seoc0924	1V	0.01
ncrc6871	1V	0.01
seob3360	1V	0.01
mioc0140	1V	0.01
mioa6121	1V	0.01
ncr9373	1V	0.01
mioa0482	1V	0.01
seoa4040	1V	0.01
fcr2611	1V	0.01
fcr3599	1V	0.01
fcr4639	1V	0.01
fcrb2421	1V	0.01
fcrb2704	1V	0.01
fcrb3309	1V	0.01
fcrb3554	1V	0.01
fcrb3644	1V	0.01
fcrb4504	1V	0.01
fcrb6780	1V	0.01
fcrb8732	1V	0.01
fcrc3538	1V	0.01
fcrc6374	1V	0.01
hfcrc5604	1V	0.01
mioa9630	1V	0.01
miod1532	1V	0.01
miod1809	1V	0.01
miod5349	1V	0.01
ncr5568	1V	0.01
ncr9933	1V	0.01
ncrc0729	1V	0.01
ncrc0852	1V	0.01
ncrc9024	1V	0.01
seoa2765	1V	0.01
seoa3359	1V	0.01
seoa4587	1V	0.01
seoa8783	1V	0.01
seoa9287	1V	0.01
seob2750	1V	0.01
seob3751	1V	0.01
seob5658	1V	0.01
seob9820	1V	0.01
seoc0416	1V	0.01
seoc1311	1V	0.01
seoc4132	1V	0.01
fcrb5000	1V	0.01

seoa0823	1V	0.01
seob9435	1V	0.01
mioc4280	1V	0.01
seoc4436	1V	0.01
mioa5059	1V	0.01
ncrc1606	1V	0.01
mioc1379	1V	0.01
miob0939	1V	0.01
fcr2582	1V	0.01
fcrb0146	1V	0.01
fcrb1689	1V	0.01
fcrb2017	1V	0.01
fcrb3576	1V	0.01
fcrb3725	1V	0.01
fcrb3760	1V	0.01
fcrb4266	1V	0.01
fcrb4543	1V	0.01
fcrb5448	1V	0.01
fcrb5687	1V	0.01
fcrb5690	1V	0.01
fcrb5720	1V	0.01
fcrb5774	1V	0.01
fcrb6281	1V	0.01
fcrb7871	1V	0.01
fcrb8202	1V	0.01
fcrb8222	1V	0.01
fcrb8802	1V	0.01
fcrb8829	1V	0.01
fcrb9858	1V	0.01
fcrc0241	1V	0.01
fcrc3488	1V	0.01
fcrc4054	1V	0.01
fcrc5040	1V	0.01
fcrc5789	1V	0.01
fcrc6184	1V	0.01
hfcrc3043	1V	0.01
hfcrc3441	1V	0.01
hfcrc3592	1V	0.01
hfcrc5706	1V	0.01
hfcrc5798	1V	0.01
mioa1370	1V	0.01
mioa1976	1V	0.01
mioa4552	1V	0.01
mioa5045	1V	0.01
mioa5054	1V	0.01
mioa5355	1V	0.01
mioa7015	1V	0.01
miob1506	1V	0.01
miob2093	1V	0.01
miob4401	1V	0.01
miob5491	1V	0.01
miob6610	1V	0.01
miob8830	1V	0.01
miob9714	1V	0.01
mioc1560	1V	0.01
mioc2039	1V	0.01
mioc2343	1V	0.01
mioc2806	1V	0.01
mioc4526	1V	0.01
mioc4839	1V	0.01
mioc7381	1V	0.01
mioc7863	1V	0.01
miod5884	1V	0.01
miod6162	1V	0.01

miod7066	1V	0.01	ncr6170	1V	0.02
ncr0007	1V	0.01	ncr9487	1V	0.02
ncr0912	1V	0.01	ncrb0262	1V	0.02
ncr3219	1V	0.01	ncrb8220	1V	0.02
ncr3649	1V	0.01	ncrc0856	1V	0.02
ncr3686	1V	0.01	ncrc4903	1V	0.02
ncr3948	1V	0.01	seoa6867	1V	0.02
ncr4384	1V	0.01	seob1144	1V	0.02
ncr5971	1V	0.01	seob2156	1V	0.02
ncr7295	1V	0.01	seob2966	1V	0.02
ncrc1498	1V	0.01	seoc0651	1V	0.02
ncrc1999	1V	0.01	seoc1476	1V	0.02
ncrc4586	1V	0.01	ncrc4531	1V	0.02
ncrc8903	1V	0.01	seoc4135	1V	0.02
ncrc9039	1V	0.01	fcrc6888	1V	0.02
seoa2162	1V	0.01	hfcr3019	1V	0.02
seoa2244	1V	0.01	mioa8096	1V	0.02
seoa3417	1V	0.01	ncrc4882	1V	0.02
seoa4783	1V	0.01	seoa9959	1V	0.02
seoa5691	1V	0.01	seoa1263	1V	0.02
seoa7543	1V	0.01	seoa7926	1V	0.02
seoa9209	1V	0.01	miob9348	1V	0.02
seob0971	1V	0.01	mioc2728	1V	0.02
seob1007	1V	0.01	ncrc4302	1V	0.02
seob1737	1V	0.01	miob8650	1V	0.02
seob1770	1V	0.01	ncrb4428	1V	0.02
seob2108	1V	0.01	ncrc4188	1V	0.02
seob3154	1V	0.01	ncrc5738	1V	0.02
seob3244	1V	0.01	seob1161	1V	0.02
seob3404	1V	0.01	seob5711	1V	0.02
seob4079	1V	0.01	fcrc6989	1V	0.02
seob5004	1V	0.01	fcr0018	1V	0.02
seob5144	1V	0.01	fcr1984	1V	0.02
seob5225	1V	0.01	fcrb1477	1V	0.02
seob9122	1V	0.01	fcrb2624	1V	0.02
seob9574	1V	0.01	mioa0763	1V	0.02
seoc1023	1V	0.01	mioa1701	1V	0.02
seoc1305	1V	0.01	mioa9792	1V	0.02
seoc4609	1V	0.01	miob3690	1V	0.02
ncrb8752	1V	0.01	mioc2341	1V	0.02
fcrb2133	1V	0.01	mioc7774	1V	0.02
seoa4675	1V	0.01	miod0993	1V	0.02
seoc2248	1V	0.01	ncr5485	1V	0.02
miod2845	1V	0.01	ncr5871	1V	0.02
fcrc6041	1V	0.01	ncr7351	1V	0.02
miob9176	1V	0.01	seoa1102	1V	0.02
seoa1559	1V	0.01	seoa6395	1V	0.02
seoc0276	1V	0.02	seoa7115	1V	0.02
ncrc1949	1V	0.02	seoa7902	1V	0.02
seob0783	1V	0.02	seoa8547	1V	0.02
miod7243	1V	0.02	seob2148	1V	0.02
fcr0529	1V	0.02	seob5395	1V	0.02
fcrb1898	1V	0.02	seoc1996	1V	0.02
fcrb2719	1V	0.02	seoc2487	1V	0.02
fcrb4542	1V	0.02	miob8373	1V	0.02
fcrb4826	1V	0.02	fcrb2437	1V	0.02
fcrb7939	1V	0.02	miob9404	1V	0.02
hfcr4168	1V	0.02	hfcr2524	1V	0.02
miob2492	1V	0.02	seoa0238	1V	0.02
miob3898	1V	0.02	miod0500	1V	0.02
miob6226	1V	0.02	seob1787	1V	0.02
mioc2546	1V	0.02	fcrb3330	1V	0.02
mioc8206	1V	0.02	ncrc3908	1V	0.02
ncr0075	1V	0.02	fcrc6542	1V	0.02

miob6702	1V	0.02	seoa9445	1V	0.02
fcrc2254	1V	0.02	seoc0705	1V	0.02
seob0752	1V	0.02	miob3131	1V	0.02
fcrb2556	1V	0.02	fcrb2334	1V	0.02
seoc0203	1V	0.02	ncrc3464	1V	0.02
ncr0252	1V	0.02	miod7461	1V	0.02
ncr3483	1V	0.02	ncr2160	1V	0.02
seoa5090	1V	0.02	fcr2182	1V	0.02
seoa8902	1V	0.02	fcrb1916	1V	0.02
fcr1992	1V	0.02	fcrb9849	1V	0.02
miob9848	1V	0.02	fcrc5873	1V	0.02
seoa5766	1V	0.02	hfcr1371	1V	0.02
mioc7084	1V	0.02	mioa1068	1V	0.02
fcrb8682	1V	0.02	mioa3629	1V	0.02
fcrc0287	1V	0.02	miob0189	1V	0.02
fcr0796	1V	0.02	miob3271	1V	0.02
fcrb3946	1V	0.02	miob4322	1V	0.02
fcrb5346	1V	0.02	miob6536	1V	0.02
fcrb8516	1V	0.02	miob9065	1V	0.02
fcrc2710	1V	0.02	mioc0337	1V	0.02
fcrc7057	1V	0.02	mioc3716	1V	0.02
mioa5409	1V	0.02	mioc6987	1V	0.02
miob1493	1V	0.02	mioc7421	1V	0.02
miob1774	1V	0.02	mioc8368	1V	0.02
miob2448	1V	0.02	miod0992	1V	0.02
miob8077	1V	0.02	ncr3339	1V	0.02
mioc4089	1V	0.02	ncr8314	1V	0.02
mioc7296	1V	0.02	ncrb0624	1V	0.02
mioc8635	1V	0.02	ncrc2763	1V	0.02
miod6731	1V	0.02	ncrc3735	1V	0.02
ncr3975	1V	0.02	ncrc9557	1V	0.02
ncr9975	1V	0.02	seoa0470	1V	0.02
ncrb6581	1V	0.02	seoa1118	1V	0.02
ncrb8619	1V	0.02	seoa8229	1V	0.02
ncrc7038	1V	0.02	seoa8716	1V	0.02
ncrc8856	1V	0.02	seob3670	1V	0.02
seoa0145	1V	0.02	seob9241	1V	0.02
seoa0420	1V	0.02	seoc0780	1V	0.02
seob2081	1V	0.02	seoc1504	1V	0.02
seob6879	1V	0.02	seob9898	1V	0.02
seob7505	1V	0.02	miob7435	1V	0.02
seob9617	1V	0.02	ncrc5631	1V	0.02
fcrb6834	1V	0.02	mioa4548	1V	0.02
fcrb8334	1V	0.02	ncr3944	1V	0.02
seob1238	1V	0.02	mioa1660	1V	0.02
seob8241	1V	0.02	seob3025	1V	0.02
miob8391	1V	0.02	hfcr2890	1V	0.02
seoa5302	1V	0.02	fcrb3539	1V	0.02
ncr0045	1V	0.02	ncr8780	1V	0.02
mioa4318	1V	0.02	ncrc1310	1V	0.02
ncrc7049	1V	0.02	seob0678	1V	0.02
miod4759	1V	0.02	mioc8793	1V	0.02
fcrb3298	1V	0.02	fcrb2591	1V	0.02
ncr0761	1V	0.02	ncr4648	1V	0.02
miod5682	1V	0.02	ncrc7065	1V	0.02
seob8386	1V	0.02	fcrc6138	1V	0.02
ncr8199	1V	0.02	fcrb9407	1V	0.02
ncrb8649	1V	0.02	ncrb3284	1V	0.02
miob9462	1V	0.02	miob4221	1V	0.02
ncr2905	1V	0.02	seob5032	1V	0.02
mioa1353	1V	0.02	ncrc0423	1V	0.02
mioa8925	1V	0.02	fcrb6990	1V	0.02
seob3131	1V	0.02	miob7268	1V	0.02
mioc8057	1V	0.02	seoa6226	1V	0.02

ncrc4296	1V	0.02
mioc1992	1V	0.02
mioc1248	1V	0.02
miod5655	1V	0.02
seob2555	1V	0.02
fcrb1733	1V	0.02
fcrb1929	1V	0.02
mioa4674	1V	0.02
mioa5695	1V	0.02
seob6030	1V	0.02
seoc2670	1V	0.02
miob3552	1V	0.02
fcrb2015	1V	0.02
fcrb7392	1V	0.02
fcrc5713	1V	0.02
hfcrc2789	1V	0.02
hfcrc4278	1V	0.02
mioa0577	1V	0.02
mioa6552	1V	0.02
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miob2700	1V	0.02
miob2855	1V	0.02
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ncr9039	1V	0.02
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ncrc3541	1V	0.02
ncrc3713	1V	0.02
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seoa0511	1V	0.02
seoa2178	1V	0.02
seoa7249	1V	0.02
seob0466	1V	0.02
seob1318	1V	0.02
seob3189	1V	0.02
seob3415	1V	0.02
seob3564	1V	0.02
seob6541	1V	0.02
seoc1069	1V	0.02
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fcrb5313	1V	0.02
seoa3852	1V	0.02
mioa3923	1V	0.02
seoa4317	1V	0.02
fcrc2683	1V	0.02
fcrb1618	1V	0.02
fcrb1320	1V	0.02
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hfcrc3726	1V	0.02
seob6853	1V	0.02
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fcrc4851	1V	0.02
fcrc5233	1V	0.02
seob2090	1V	0.02
fcrc0959	1V	0.02

ncrc2087	1V	0.02
ncr3598	1V	0.02
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mioc2536	1V	0.02
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mioa4770	1V	0.03
ncrb2588	1V	0.03
fcr5930	1V	0.03
fcr1092	1V	0.03
fcrb1962	1V	0.03
fcrb4506	1V	0.03
fcrc5205	1V	0.03
hfcrc2658	1V	0.03
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mioa5594	1V	0.03
miob1778	1V	0.03
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miob4793	1V	0.03
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mioc9974	1V	0.03
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ncrb1186	1V	0.03
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ncrc4467	1V	0.03
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seoa5575	1V	0.03
seoa7443	1V	0.03
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seob0376	1V	0.03
seob1100	1V	0.03
seob1667	1V	0.03
seob4440	1V	0.03
seob7465	1V	0.03
seob8817	1V	0.03
seob9001	1V	0.03
fcrb9583	1V	0.03
seob7047	1V	0.03
fcrb8649	1V	0.03
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fcrc6313	1V	0.03
ncr2866	1V	0.03
ncrc5758	1V	0.03
ncrc2868	1V	0.03
ncrc0421	1V	0.03
ncrc2018	1V	0.03
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seob6584	1V	0.03
miob3942	1V	0.03
miod7460	1V	0.03
fcrb4551	1V	0.03
fcrb1921	1V	0.03
mioc0347	1V	0.03
fcrb2569	1V	0.03
miob0931	1V	0.03
seob7463	1V	0.03
fcrb7831	1V	0.03

mioc8412	1V	0.03	seob2810	1V	0.03
fcrb6650	1V	0.03	mioc7665	1V	0.03
seob1538	1V	0.03	miob8531	1V	0.03
fcrc6476	1V	0.03	hfcr1238	1V	0.03
seoa5162	1V	0.03	ncr3701	1V	0.03
mioa0601	1V	0.03	ncrb3957	1V	0.03
miod4449	1V	0.03	seob3654	1V	0.03
miod5591	1V	0.03	seob3367	1V	0.03
seob5562	1V	0.03	fcrc5516	1V	0.03
fcrb8095	1V	0.03	fcrb6897	1V	0.03
fcr1182	1V	0.03	ncrc3536	1V	0.03
fcr2196	1V	0.03	fcr1004	1V	0.03
fcrb1411	1V	0.03	fcrb1741	1V	0.03
fcrb6436	1V	0.03	fcrb4918	1V	0.03
fcrb7593	1V	0.03	fcr1098	1V	0.03
fcrc0730	1V	0.03	fcr1855	1V	0.03
fcrc5174	1V	0.03	fcr3121	1V	0.03
fcrc6010	1V	0.03	fcr3155	1V	0.03
hfcr2314	1V	0.03	fcr4699	1V	0.03
hfcr2963	1V	0.03	fcrb1724	1V	0.03
hfcr5150	1V	0.03	fcrb2554	1V	0.03
mioa4476	1V	0.03	fcrb2866	1V	0.03
miob2478	1V	0.03	fcrb4238	1V	0.03
mioc7225	1V	0.03	fcrb4331	1V	0.03
mioc7952	1V	0.03	fcrb4788	1V	0.03
miod0708	1V	0.03	fcrb5267	1V	0.03
miod1389	1V	0.03	fcrb6106	1V	0.03
miod5651	1V	0.03	fcrb6236	1V	0.03
miod6835	1V	0.03	fcrb6416	1V	0.03
ncr0644	1V	0.03	fcrb6636	1V	0.03
ncr3165	1V	0.03	fcrb6640	1V	0.03
ncr3830	1V	0.03	fcrb6802	1V	0.03
ncr3869	1V	0.03	fcrb6939	1V	0.03
ncr4040	1V	0.03	fcrb6968	1V	0.03
ncr8326	1V	0.03	fcrb7068	1V	0.03
ncrb0487	1V	0.03	fcrb7951	1V	0.03
ncrb1956	1V	0.03	fcrb8927	1V	0.03
ncrb5537	1V	0.03	fcrb9639	1V	0.03
ncrb7516	1V	0.03	fcrc0148	1V	0.03
ncrb8721	1V	0.03	fcrc2577	1V	0.03
ncrc1003	1V	0.03	fcrc6460	1V	0.03
ncrc3842	1V	0.03	hfcr4046	1V	0.03
ncrc6268	1V	0.03	mioa2528	1V	0.03
ncrc6996	1V	0.03	mioa2986	1V	0.03
seoa0040	1V	0.03	mioa5231	1V	0.03
seoa4886	1V	0.03	mioa8679	1V	0.03
seoa5382	1V	0.03	mioa8984	1V	0.03
seoa5473	1V	0.03	mioa9709	1V	0.03
seoa9421	1V	0.03	miob0942	1V	0.03
seob1891	1V	0.03	miob2593	1V	0.03
seob9635	1V	0.03	miob3668	1V	0.03
seoc1694	1V	0.03	miob4975	1V	0.03
seoc2172	1V	0.03	miob7274	1V	0.03
seoc3029	1V	0.03	miob8932	1V	0.03
ncrc4991	1V	0.03	miob9274	1V	0.03
miod1714	1V	0.03	mioc0107	1V	0.03
ncr2079	1V	0.03	mioc1025	1V	0.03
mioc6358	1V	0.03	mioc1135	1V	0.03
mioa8484	1V	0.03	mioc1865	1V	0.03
ncrc1775	1V	0.03	mioc3243	1V	0.03
fcrb7616	1V	0.03	mioc3565	1V	0.03
fcr0833	1V	0.03	mioc3571	1V	0.03
seob4223	1V	0.03	mioc7073	1V	0.03
seob2689	1V	0.03	mioc7542	1V	0.03



mioc7910	1V	0.03
miod0884	1V	0.03
miod5190	1V	0.03
miod6745	1V	0.03
ncr0927	1V	0.03
ncr2583	1V	0.03
ncr2848	1V	0.03
ncr3148	1V	0.03
ncr5055	1V	0.03
ncr5301	1V	0.03
ncr9469	1V	0.03
ncrb6432	1V	0.03
ncrb8714	1V	0.03
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ncrc4263	1V	0.03
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fcrb4388	1V	0.04
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ncr2486	1V	0.04
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fcr0997	1V	0.04
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fcr3286	1V	0.04
fcr4743	1V	0.04
fcrb1466	1V	0.04
fcrb2859	1V	0.04
fcrb3080	1V	0.04
fcrc0810	1V	0.04
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fcrc5071	1V	0.04	ncrc0115	1X	3.19e-04
seob1319	1V	0.04	fcrb5002	1X	4.23e-04
ncr5168	1V	0.04	seoc4941	1X	4.34e-04
seob8660	1V	0.04	mioa3486	1X	4.38e-04
fcrb5177	1V	0.04	seoa5849	1X	4.42e-04
ncrc9530	1V	0.04	mioc6412	1X	4.44e-04
fcrb2150	1V	0.04	seob0514	1X	4.46e-04
fcr1562	1V	0.04	miob7985	1X	4.6e-04
ncr3118	1V	0.04	ncrb8396	1X	4.66e-04
ncrb2360	1V	0.04	ncrc6479	1X	4.81e-04
fcrb8940	1V	0.04	ncr7973	1X	4.85e-04
fcrb1446	1V	0.04	hfcr3183	1X	4.88e-04
seoa7295	1V	0.04	seoc2336	1X	4.94e-04
miob8146	1V	0.04	seoa9792	1X	5.09e-04
seoa7223	1V	0.04	fcrc5384	1X	5.1e-04
ncrc1349	1V	0.04	mioc2694	1X	5.18e-04
fcrb2763	1V	0.04	mioc0276	1X	5.28e-04
fcrb6747	1V	0.04	seoa5528	1X	5.38e-04
mioa0869	1V	0.04	seoa9287	1X	5.45e-04
fcrb1312	1V	0.04	seoc4380	1X	6.07e-04
mioc4834	1V	0.04	miod6162	1X	6.12e-04
miob9463	1X	3.09e-07	miod6147	1X	6.2e-04
fcrb6460	1X	8.2e-07	seob9847	1X	6.68e-04
fcrb5214	1X	1.04e-06	ncrb8220	1X	7.0e-04
fcrc2954	1X	1.71e-06	mioc1025	1X	7.12e-04
fcrb3521	1X	4.14e-06	miob7850	1X	7.18e-04
seoc4135	1X	4.17e-06	seoc4971	1X	7.29e-04
mioc2039	1X	4.36e-06	fcrc5671	1X	7.36e-04
ncrc9739	1X	1.55e-05	seoc4381	1X	7.54e-04
miob9748	1X	1.57e-05	seoc4132	1X	8.23e-04
miod6961	1X	1.97e-05	mioc2514	1X	8.4e-04
fcrb4981	1X	3.15e-05	hfcr2890	1X	9.18e-04
ncrb0074	1X	3.45e-05	seob4515	1X	9.22e-04
ncr5651	1X	3.54e-05	seoa7249	1X	9.92e-04
fcrb9611	1X	3.57e-05	seoc1675	1X	1.027088e-03
fcr1169	1X	3.6e-05	ncr0133	1X	1.05172e-03
seoa9389	1X	3.72e-05	miob9805	1X	1.156892e-03
ncrc1140	1X	3.81e-05	seoa9042	1X	1.158959e-03
mioc2094	1X	3.97e-05	fcrb9849	1X	1.227294e-03
mioa7976	1X	4.01e-05	miob9831	1X	1.263821e-03
ncrc4931	1X	4.13e-05	hfcr4489	1X	1.264067e-03
miod6134	1X	4.56e-05	ncr4673	1X	1.338044e-03
fcrc5482	1X	6.75e-05	fcrb7852	1X	1.34787e-03
fcrb6664	1X	7.04e-05	fcrc2573	1X	1.392684e-03
fcrc6826	1X	8.11e-05	seob3307	1X	1.439442e-03
miob8825	1X	9.0e-05	fcrc2429	1X	1.448948e-03
fcrb5855	1X	9.3e-05	fcrc5850	1X	1.455176e-03
fcrb7055	1X	1.05e-04	seob7739	1X	1.615597e-03
mioa2377	1X	1.05e-04	seob9756	1X	1.643381e-03
miod5894	1X	1.05e-04	miob9340	1X	1.687009e-03
ncrb8207	1X	1.06e-04	fcrb6469	1X	1.855844e-03
mioc0206	1X	1.09e-04	mioc2388	1X	1.89135e-03
seob9884	1X	1.24e-04	seoc1561	1X	1.894109e-03
fcrc5452	1X	1.31e-04	fcrc2082	1X	1.897321e-03
miob7391	1X	1.32e-04	seob5726	1X	1.905436e-03
fcrc6174	1X	1.37e-04	seoc3690	1X	1.972802e-03
ncr8725	1X	1.44e-04	miob5434	1X	1.991278e-03
fcrb4985	1X	1.54e-04	fcrb7722	1X	2.042772e-03
mioc2021	1X	1.67e-04	ncr7286	1X	2.102525e-03
miob9614	1X	1.96e-04	miod7440	1X	2.149284e-03
seoc4928	1X	2.44e-04	seob2990	1X	2.157379e-03
fcrc4390	1X	2.52e-04	miob8026	1X	2.175933e-03
ncrb6903	1X	2.65e-04	ncr7292	1X	2.18489e-03
mioc0107	1X	2.66e-04	seoa6314	1X	2.307802e-03

seob5894	1X	2.313364e-03	miob9734	1X	5.792326e-03
ncrb8189	1X	2.367011e-03	seoc0369	1X	5.805794e-03
ncrc1003	1X	2.407968e-03	mioa4109	1X	5.817645e-03
mioa8945	1X	2.42255e-03	seoa2300	1X	5.821371e-03
fcrb7829	1X	2.472346e-03	ncrc5375	1X	5.858062e-03
mioa6091	1X	2.513592e-03	fcrc6697	1X	5.891967e-03
mioc5740	1X	2.55859e-03	seob5240	1X	5.949332e-03
fcrc5107	1X	2.595298e-03	fcrc6898	1X	6.102757e-03
miod5703	1X	2.632329e-03	mioa4241	1X	6.102757e-03
fcrb1724	1X	2.708883e-03	mioa4245	1X	6.102757e-03
mioa8778	1X	2.736234e-03	fcrc5355	1X	6.12294e-03
seoc4436	1X	2.749055e-03	seob4117	1X	6.194381e-03
miod2330	1X	2.768542e-03	fcrc4663	1X	6.213654e-03
miob9652	1X	2.773751e-03	seob4067	1X	6.309695e-03
seob9772	1X	2.86764e-03	seob9872	1X	6.406966e-03
seoc4137	1X	2.947972e-03	mioc1088	1X	6.432154e-03
mioc7304	1X	2.982148e-03	mioa4229	1X	6.506475e-03
seoc0616	1X	3.08994e-03	seoc1432	1X	6.543795e-03
ncr3262	1X	3.123964e-03	fcrc1654	1X	6.589598e-03
ncrc5653	1X	3.128058e-03	miod5256	1X	6.623723e-03
fcrb5892	1X	3.158737e-03	mioa1276	1X	6.669969e-03
mioc3261	1X	3.213251e-03	mioc7362	1X	6.725393e-03
mioc4534	1X	3.321646e-03	fcr2573	1X	6.784327e-03
seoc1234	1X	3.414658e-03	fcrb5664	1X	6.784327e-03
hfc4278	1X	3.439806e-03	miob3314	1X	6.784327e-03
seoa8979	1X	3.449583e-03	ncr3642	1X	6.784327e-03
seoc4316	1X	3.511847e-03	seoa2272	1X	6.784327e-03
seob9635	1X	3.531378e-03	seob7409	1X	6.845355e-03
fcr2821	1X	3.593158e-03	miob5770	1X	6.867442e-03
hfc3500	1X	3.661254e-03	fcrb3466	1X	6.869457e-03
fcr4460	1X	3.716445e-03	seoc2264	1X	6.927055e-03
hfc4423	1X	3.861046e-03	seob6558	1X	7.08591e-03
miob5098	1X	3.86132e-03	ncrb4039	1X	7.185379e-03
mioa1473	1X	3.958354e-03	fcrb3966	1X	7.202047e-03
mioa1674	1X	3.965367e-03	seoa0393	1X	7.211102e-03
seoc1495	1X	4.012337e-03	ncr7967	1X	7.237351e-03
miob2448	1X	4.055375e-03	ncrb0164	1X	7.331552e-03
miob8694	1X	4.122295e-03	fcrc5458	1X	7.482432e-03
fcrb3219	1X	4.135014e-03	ncr2575	1X	7.600247e-03
seoa1615	1X	4.220231e-03	ncrc4295	1X	7.627364e-03
ncrc0644	1X	4.272698e-03	seob1318	1X	7.684111e-03
seoc0551	1X	4.340756e-03	fcrc0651	1X	7.699131e-03
fcrb8973	1X	4.544509e-03	fcrb6676	1X	7.719631e-03
fcrc2710	1X	4.544509e-03	fcrb8536	1X	7.719631e-03
ncr5027	1X	4.544509e-03	mioa8987	1X	7.719631e-03
seoa8960	1X	4.572134e-03	seoa0158	1X	7.719631e-03
seoa5746	1X	4.64536e-03	seoa5933	1X	7.719631e-03
fcrb4937	1X	4.846074e-03	seoa8239	1X	7.719631e-03
seoc1078	1X	4.922685e-03	seob5395	1X	7.719631e-03
seoc0284	1X	5.076305e-03	miod1718	1X	8.034424e-03
mioc7952	1X	5.107777e-03	mioc3549	1X	8.160964e-03
fcrb6718	1X	5.108963e-03	seoc4260	1X	8.363871e-03
fcrb1657	1X	5.130499e-03	mioa3572	1X	8.372463e-03
ncrc0852	1X	5.205548e-03	seob9820	1X	8.388595e-03
ncrc5947	1X	5.205548e-03	mioa1948	1X	8.415321e-03
seoa3359	1X	5.205548e-03	seoc2191	1X	8.433017e-03
miod4522	1X	5.216795e-03	seoa7295	1X	8.440913e-03
fcrb8187	1X	5.219732e-03	fcrb7118	1X	8.491482e-03
fcr5509	1X	5.329617e-03	mioc2872	1X	8.598424e-03
seob0918	1X	5.361021e-03	fcr1337	1X	8.6173e-03
miob7136	1X	5.450311e-03	ncrc3593	1X	8.6173e-03
miod5198	1X	5.472689e-03	ncr0420	1X	8.718204e-03
ncrb2588	1X	5.579537e-03	seoa2472	1X	8.76281e-03
mioc5179	1X	5.601724e-03	fcrb6693	1X	8.764987e-03

fcrb7072	1X	8.764987e-03	fcrb6015	1X	0.01
hfcrc6256	1X	8.764987e-03	fcrc7047	1X	0.01
miob3898	1X	8.764987e-03	mioa1392	1X	0.01
miob5855	1X	8.764987e-03	ncr5522	1X	0.01
miod0625	1X	8.764987e-03	fcrb9520	1X	0.01
ncrc6813	1X	8.764987e-03	fcrc0959	1X	0.01
seoa0511	1X	8.764987e-03	mioc7216	1X	0.01
mioc4843	1X	8.811966e-03	fcrb3841	1X	0.01
mioc6211	1X	8.904696e-03	ncr0107	1X	0.01
seob6256	1X	9.02746e-03	miob9325	1X	0.01
mioc0121	1X	9.163151e-03	seoa1036	1X	0.01
fcrb8730	1X	9.169484e-03	mioa5231	1X	0.01
fcrb9858	1X	9.20164e-03	fcrb1909	1X	0.01
seoa4324	1X	9.212171e-03	mioa3084	1X	0.01
miob8947	1X	9.337599e-03	ncr6415	1X	0.01
miob2533	1X	9.353064e-03	mioa1293	1X	0.01
mioa8831	1X	9.438617e-03	mioa6721	1X	0.01
seoc2295	1X	9.611484e-03	miob3696	1X	0.01
miod7081	1X	9.612646e-03	mioc2928	1X	0.01
seob0906	1X	9.62924e-03	ncrb3352	1X	0.01
ncrc4448	1X	9.709792e-03	ncrc1331	1X	0.01
fcrc2613	1X	9.72871e-03	ncrc3596	1X	0.01
mioc6997	1X	9.740521e-03	seoa5382	1X	0.01
seoc1628	1X	9.782377e-03	seoa6203	1X	0.01
miob4668	1X	9.926235e-03	seob8291	1X	0.01
fcrc5139	1X	9.930809e-03	seob0058	1X	0.01
fcrc5468	1X	9.930809e-03	mioc2443	1X	0.01
miob3591	1X	9.930809e-03	seoc0778	1X	0.01
mioc3107	1X	9.930809e-03	miob8639	1X	0.01
ncrc1192	1X	9.930809e-03	fcr3599	1X	0.01
seoa6661	1X	9.930809e-03	hfcrc2250	1X	0.01
seoc4609	1X	9.930809e-03	ncrc3520	1X	0.01
miob7290	1X	9.963579e-03	mioa3528	1X	0.01
ncr2861	1X	0.01	fcrb1788	1X	0.01
miob9185	1X	0.01	fcrb3782	1X	0.01
seoa2381	1X	0.01	fcrb9856	1X	0.01
fcrb5122	1X	0.01	ncrc3773	1X	0.01
miob8992	1X	0.01	ncrc4728	1X	0.01
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seob5209	1X	0.01	seob3654	1X	0.01
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fcrb8719	1X	0.01	mioc2074	1X	0.01
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fcrc5086	1X	0.01	fcr1347	1X	0.01
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mioc2634	1X	0.01	miod0992	1X	0.01
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fcr2986	1X	0.01	seob8807	1X	0.01
miod6835	1X	0.01	seob9368	1X	0.01
miod4564	1X	0.01	seoa1736	1X	0.01
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miob7531	1X	0.01	mioa8096	1X	0.01

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fcrb8910	1X	0.01
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miob9348	1X	0.01
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ncrb3980	1X	0.01
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seob4734	1X	0.03
fcrb3017	1X	0.03
fcrb4533	1X	0.03
fcrb4921	1X	0.03
miob4822	1X	0.03
miob8143	1X	0.03
mioc7904	1X	0.03
seob0298	1X	0.03
mioc2188	1X	0.03
hfcr4114	1X	0.03
ncr2930	1X	0.03
miob2968	1X	0.03
fcrb3074	1X	0.03
ncr4545	1X	0.03
miod4686	1X	0.03
seob2974	1X	0.03
seob3564	1X	0.03
fcr3173	1X	0.03
fcrb1898	1X	0.03
fcrb2546	1X	0.03
fcrb5077	1X	0.03
fcrb5754	1X	0.03
fcrb9499	1X	0.03
fcrc2830	1X	0.03
fcrc5154	1X	0.03
fcrc5282	1X	0.03
miob8657	1X	0.03
mioc0375	1X	0.03
mioc3092	1X	0.03
mioc5226	1X	0.03
miod4493	1X	0.03
ncr1692	1X	0.03
ncrb0624	1X	0.03
ncrc1361	1X	0.03
seoa0420	1X	0.03
seoa1924	1X	0.03
seoa6178	1X	0.03
seoa6654	1X	0.03

seob1273	1X	0.03
seob2689	1X	0.03
seoc0034	1X	0.03
seoc4888	1X	0.03
ncrc1193	1X	0.03
ncrb1179	1X	0.03
fcrc6011	1X	0.03
ncr3869	1X	0.03
fcrb3760	1X	0.03
miob2287	1X	0.03
mioc7863	1X	0.03
miod1236	1X	0.03
ncrc0185	1X	0.03
ncrc9947	1X	0.03
seob0085	1X	0.03
seob2259	1X	0.03
seob6000	1X	0.03
fcrb4869	1X	0.03
fcrb6220	1X	0.03
fcrc5577	1X	0.03
miob3348	1X	0.03
mioc1125	1X	0.03
ncrc1421	1X	0.03
ncrc3100	1X	0.03
ncrc5079	1X	0.03
fcrb8340	1X	0.03
fcrb8700	1X	0.03
ncr7934	1X	0.03
seoc3965	1X	0.03
seob8104	1X	0.03
seoa5691	1X	0.03
fcrc4150	1X	0.03
seob2775	1X	0.03
seob8065	1X	0.03
mioc3042	1X	0.04
seoc0149	1X	0.04
hfcr2616	1X	0.04
seoa3717	1X	0.04
ncr4485	1X	0.04
ncrb1337	1X	0.04
fcrb3086	1X	0.04
fcrc6374	1X	0.04
fcrb4249	1X	0.04
fcrb5702	1X	0.04
fcr4784	1X	0.04
fcrb5100	1X	0.04
fcrc0213	1X	0.04
fcrc1431	1X	0.04
mioa0311	1X	0.04
miob2355	1X	0.04
miob9053	1X	0.04
mioc0902	1X	0.04
mioc3958	1X	0.04
miod1291	1X	0.04
miod1389	1X	0.04
ncr3268	1X	0.04
ncr4215	1X	0.04
ncr4550	1X	0.04
ncr7136	1X	0.04
ncr8234	1X	0.04
ncr9502	1X	0.04
ncrb1186	1X	0.04
ncrb2517	1X	0.04
ncrb8539	1X	0.04

ncrc1596	1X	0.04	fcrc5835	1X	0.04
ncrc1885	1X	0.04	hfcr4477	1X	0.04
ncrc2529	1X	0.04	mioa2478	1X	0.04
ncrc3713	1X	0.04	mioa2993	1X	0.04
ncrc4016	1X	0.04	mioa4542	1X	0.04
ncrc4740	1X	0.04	mioa5511	1X	0.04
ncrc6371	1X	0.04	mioa6262	1X	0.04
ncrc9819	1X	0.04	miob3307	1X	0.04
seoa0085	1X	0.04	miob7106	1X	0.04
seoa5894	1X	0.04	mioc5661	1X	0.04
seob0266	1X	0.04	miod0080	1X	0.04
seob0949	1X	0.04	ncr3727	1X	0.04
seob4579	1X	0.04	ncr5668	1X	0.04
seob8885	1X	0.04	ncrc5738	1X	0.04
seob9193	1X	0.04	ncrc7005	1X	0.04
seoc2192	1X	0.04	ncrc9286	1X	0.04
seoc3487	1X	0.04	seoa3269	1X	0.04
ncrc9401	1X	0.04	seoa3989	1X	0.04
fcrb4570	1X	0.04	seoa9494	1X	0.04
mioa3469	1X	0.04	seob0700	1X	0.04
miob1789	1X	0.04	seob4498	1X	0.04
mioc1438	1X	0.04	seob5632	1X	0.04
ncr3040	1X	0.04	seoc1476	1X	0.04
ncrc0262	1X	0.04	seoc2220	1X	0.04
seoa0101	1X	0.04	seoc5267	1X	0.04
seoa3633	1X	0.04	miob9209	1X	0.04
hfcr6406	1X	0.04	miod6038	1X	0.04
miob3809	1X	0.04	ncrb8437	1X	0.04
ncr5046	1X	0.04	fcrb5007	1X	0.04
seoa7296	1X	0.04	seob6020	1X	0.04
seob2139	1X	0.04	fcrb5199	1X	0.04
mioc1808	1X	0.04	miob4760	1X	0.04
seoc4625	1X	0.04	miob9010	1X	0.04
mioc0227	1X	0.04	ncrb2125	1X	0.04
ncrc0457	1X	0.04	fcrb9680	1X	0.04
seob6835	1X	0.04	fcrb1580	1X	0.04
mioa3646	1X	0.04	ncrb0364	1X	0.04
seoa2795	1X	0.04	seob5684	1X	0.04
seoc2622	1X	0.04	mioa2319	1X	0.04
hfcr4488	1X	0.04	seob0831	1X	0.04
mioc4219	1X	0.04	ncrb2798	1X	0.04
seob1133	1X	0.04	ncrc6659	1X	0.04
miod5369	1X	0.04	seob5523	1Y	5.44e-07
fcrb6643	1X	0.04	seob6853	1Y	1.12e-06
mioc7260	1X	0.04	ncrc0262	1Y	3.34e-06
ncrc4001	1X	0.04	seoc4484	1Y	3.37e-06
ncrc9525	1X	0.04	mioa1585	1Y	8.5e-06
mioc4575	1X	0.04	ncrb2092	1Y	8.5e-06
hfcr4497	1X	0.04	seob8368	1Y	8.5e-06
mioa3399	1X	0.04	seoc1203	1Y	8.5e-06
mioa6545	1X	0.04	mioa3160	1Y	8.88e-06
fcrb1562	1X	0.04	seob8911	1Y	8.88e-06
fcrb6928	1X	0.04	miod5349	1Y	9.46e-06
fcrc6631	1X	0.04	ncrb7292	1Y	9.46e-06
miob6518	1X	0.04	miob0986	1Y	1.09e-05
ncrc4079	1X	0.04	fcr2103	1Y	1.38e-05
seoa3287	1X	0.04	fcrb3252	1Y	1.38e-05
seoc1804	1X	0.04	fcrc2090	1Y	1.38e-05
fcrc0148	1X	0.04	miob6562	1Y	1.38e-05
fcr0788	1X	0.04	mioc3430	1Y	1.38e-05
fcrb3474	1X	0.04	mioc6997	1Y	1.38e-05
fcrb6986	1X	0.04	ncr0025	1Y	1.38e-05
fcrb7440	1X	0.04	seoa2970	1Y	1.38e-05
fcrb7443	1X	0.04	seoa9373	1Y	1.38e-05

seoc1593	1Y	1.38e-05	ncr1387	1Y	2.99713e-04
fcrb8465	1Y	2.03e-05	hfcr2984	1Y	3.16106e-04
ncrc2888	1Y	2.54e-05	ncrc9286	1Y	3.16256e-04
fcr0107	1Y	2.57e-05	fcrb7830	1Y	3.26091e-04
fcrb1922	1Y	2.57e-05	miob8694	1Y	3.26091e-04
mioc2665	1Y	2.61e-05	seoa1480	1Y	3.26091e-04
fcrb7588	1Y	2.76e-05	seob3189	1Y	3.26091e-04
mioc6238	1Y	2.76e-05	seoc6703	1Y	3.26091e-04
ncrc4597	1Y	2.76e-05	ncr3163	1Y	3.28388e-04
seoa4518	1Y	2.76e-05	mioa3856	1Y	3.33477e-04
seoc2029	1Y	2.76e-05	ncr0258	1Y	3.45611e-04
fcrb8504	1Y	3.07e-05	fcr6530	1Y	3.55737e-04
fcrc3358	1Y	3.07e-05	fcr7403	1Y	3.55737e-04
miob9209	1Y	3.07e-05	fcrb2040	1Y	3.55737e-04
miob9831	1Y	3.07e-05	fcrb5326	1Y	3.55737e-04
mioc6055	1Y	3.07e-05	fcrc0076	1Y	3.55737e-04
mioc4142	1Y	3.07e-05	mioa1626	1Y	3.55737e-04
mioc4759	1Y	3.07e-05	miob4308	1Y	3.55737e-04
seoc2824	1Y	3.07e-05	ncr0251	1Y	3.55737e-04
seoa7608	1Y	3.33e-05	ncr0660	1Y	3.55737e-04
fcrc3993	1Y	3.64e-05	seoa1413	1Y	3.55737e-04
ncr0176	1Y	3.64e-05	seoc2976	1Y	3.55737e-04
seob7432	1Y	3.64e-05	mioc7421	1Y	3.63889e-04
ncrc8835	1Y	4.15e-05	seoc2696	1Y	3.63889e-04
fcrc5831	1Y	4.31e-05	mioc1203	1Y	3.76683e-04
hfcr5970	1Y	4.31e-05	fcrb9671	1Y	3.8591e-04
seob6506	1Y	4.31e-05	mioc2556	1Y	4.17224e-04
seob9960	1Y	4.31e-05	seob0523	1Y	4.48203e-04
miob8301	1Y	5.82e-05	fcrb4616	1Y	4.63478e-04
miob9533	1Y	5.82e-05	fcrb7808	1Y	4.91846e-04
ncr9956	1Y	5.82e-05	hfcr0525	1Y	4.91846e-04
seoc1996	1Y	5.82e-05	mioa2580	1Y	4.91846e-04
mioc4843	1Y	6.73e-05	ncrc3045	1Y	4.91846e-04
seoc0513	1Y	6.97e-05	ncrc4308	1Y	4.91846e-04
seoa0288	1Y	7.47e-05	seob4584	1Y	4.91846e-04
fcr3101	1Y	8.62e-05	ncr4180	1Y	5.07682e-04
seob0200	1Y	8.62e-05	miob3725	1Y	5.09895e-04
miob7099	1Y	1.04084e-04	fcrb2933	1Y	5.21225e-04
fcrb7488	1Y	1.0904e-04	fcrb3476	1Y	5.21225e-04
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ncrc2080	1Y	1.16828e-04	mioc2021	1Y	5.21225e-04
seoa4670	1Y	1.16828e-04	ncrb3541	1Y	5.21225e-04
seob9346	1Y	1.34696e-04	seoc0619	1Y	5.2253e-04
fcr1173	1Y	1.52868e-04	fcrb3140	1Y	5.6899e-04
ncrc1044	1Y	1.52868e-04	ncrc3598	1Y	5.6899e-04
seoc0920	1Y	1.57502e-04	seob1853	1Y	5.6899e-04
fcr3367	1Y	1.63813e-04	ncrc6994	1Y	6.36489e-04
ncrc4555	1Y	1.63813e-04	seoa7652	1Y	6.36489e-04
fcrc5937	1Y	1.72728e-04	fcrb8419	1Y	6.59196e-04
miob8812	1Y	1.72728e-04	mioc8507	1Y	6.59196e-04
ncr5971	1Y	1.72728e-04	seoa0783	1Y	6.59196e-04
seoa8636	1Y	1.72728e-04	seob4925	1Y	6.68896e-04
mioc1117	1Y	2.74004e-04	mioc2891	1Y	6.8067e-04
miob9404	1Y	2.94903e-04	mioc0894	1Y	7.11238e-04
mioc9205	1Y	2.94903e-04	ncrb5972	1Y	7.11238e-04
fcr2700	1Y	2.97843e-04	fcrc7112	1Y	7.18906e-04
fcr3861	1Y	2.97843e-04	mioc2792	1Y	7.42567e-04
fcrb3497	1Y	2.97843e-04	seob3158	1Y	7.46102e-04
fcrb8614	1Y	2.97843e-04	seoc7785	1Y	7.91035e-04
mioc0121	1Y	2.97843e-04	fcr0253	1Y	8.82072e-04
mioc3618	1Y	2.97843e-04	seob1660	1Y	8.82072e-04
seoa6203	1Y	2.97843e-04	seob2283	1Y	8.82072e-04
seob5748	1Y	2.97843e-04	fcrb4226	1Y	9.26956e-04
seoc1236	1Y	2.97843e-04	fcrc3416	1Y	9.27715e-04

mioa2173	1Y	9.48317e-04	seob5379	1Z	0.01
ncrc3554	1Y	9.48767e-04	seob1513	1Z	0.01
ncrc1310	1Y	9.51038e-04	hfcr3622	1Z	0.01
fcrb6478	1Y	9.59421e-04	fcrc6563	1Z	0.01
ncrb6903	1Y	1.001243e-03	miob4055	1Z	0.02
fcrb7495	1Y	1.020987e-03	seoa7509	1Z	0.02
fcrb8422	1Y	1.020987e-03	seoa6573	1Z	0.02
fcrc7219	1Y	1.020987e-03	fcrb4696	1Z	0.02
seoa2949	1Y	1.020987e-03	seob4805	1Z	0.02
seob4589	1Y	1.071134e-03	seoc1425	1Z	0.02
fcrb1492	1Y	1.115562e-03	mioc0630	1Z	0.02
hfcr2238	1Y	1.115562e-03	seob9614	1Z	0.02
seob8741	1Y	1.163938e-03	seob8501	1Z	0.02
mioa2073	1Y	1.200074e-03	miob2687	1Z	0.02
ncrc0749	1Y	1.200074e-03	ncr3778	1Z	0.02
mioc9896	1Y	1.350122e-03	mioa4014	1Z	0.02
fcrb2859	1Y	1.393429e-03	seob3751	1Z	0.02
fcrb3010	1Y	1.393429e-03	mioc0950	1Z	0.02
fcrb8432	1Y	1.393429e-03	fcrb4542	1Z	0.02
fcrc6279	1Y	1.393429e-03	seoc1230	1Z	0.02
miob3560	1Y	1.393429e-03	fcrb8504	1Z	0.02
miob9551	1Y	1.393429e-03	fcrc5351	1Z	0.02
miod1606	1Y	1.393429e-03	fcrb5254	1Z	0.02
seoa8716	1Y	1.393429e-03	mioc3580	1Z	0.02
fcrb3592	1Y	1.430199e-03	mioa7299	1Z	0.02
ncrc5230	1Y	1.443394e-03	miod4184	1Z	0.02
fcrb3015	1Y	1.449119e-03	seoc2173	1Z	0.02
ncrb8273	1Y	1.449119e-03	seoa6358	1Z	0.02
seoa9389	1Y	1.449119e-03	fcr5222	1Z	0.02
ncr9664	1Y	1.538333e-03	ncr4452	1Z	0.02
miob3161	1Y	1.541015e-03	mioc0347	1Z	0.02
miob0644	1Y	1.545534e-03	ncrc9483	1Z	0.02
seoc1872	1Y	1.553693e-03	mioa2333	1Z	0.02
ncr3815	1Y	1.615964e-03	seoc4103	1Z	0.02
seob2085	1Y	1.615964e-03	mioa1062	1Z	0.03
fcrb9588	1Z	9.42678e-04	ncrc4600	1Z	0.03
ncrc9280	1Z	1.36307e-03	seob1316	1Z	0.03
fcrc6826	1Z	1.61351e-03	seob1617	1Z	0.03
seoa1559	1Z	1.740315e-03	miod0884	1Z	0.03
ncrb8392	1Z	4.140103e-03	fcr1844	1Z	0.03
ncr4696	1Z	4.503228e-03	fcrb2160	1Z	0.03
ncrc9469	1Z	4.849487e-03	fcrc0604	1Z	0.03
fcrb9694	1Z	6.09468e-03	miob3456	1Z	0.03
ncr3559	1Z	7.002691e-03	miob4673	1Z	0.03
fcrb1950	1Z	7.501979e-03	miod1714	1Z	0.03
fcrb4925	1Z	7.651244e-03	fcrb6874	1Z	0.03
seoc2475	1Z	7.691468e-03	mioc7818	1Z	0.03
miod1505	1Z	8.44159e-03	mioa4057	1Z	0.03
seoa2391	1Z	9.669113e-03	fcrb9871	1Z	0.03
ncr0210	1Z	9.776908e-03	miob3928	1Z	0.03
fcrb9751	1Z	9.809161e-03	ncr3963	1Z	0.03
seob5773	1Z	0.01	miob3396	1Z	0.03
seoa1552	1Z	0.01	mioa1494	1Z	0.03
seoa1104	1Z	0.01	mioc1198	1Z	0.03
miob3354	1Z	0.01	miob4975	1Z	0.04
seob1793	1Z	0.01	mioa3629	1Z	0.04
seoc0951	1Z	0.01	fcr0665	1Z	0.04
seob3154	1Z	0.01	fcrb1382	1Z	0.04
mioc2619	1Z	0.01	mioa0890	1Z	0.04
seob7584	1Z	0.01	ncr3434	1Z	0.04
ncrb2395	1Z	0.01	hfcr3500	1Z	0.04
fcrb7070	1Z	0.01	fcrb1992	1Z	0.04
seob6413	1Z	0.01	mioa8774	1Z	0.04
ncrc1103	1Z	0.01	fcrb8208	1Z	0.04

ncrc4226	1Z	0.04	fcrc5351	2	0.02
seob4147	1Z	0.04	fcrb5254	2	0.02
fcr0990	1Z	0.04	mioc3580	2	0.02
fcrc7240	1Z	0.04	mioa7299	2	0.02
fcr4460	1Z	0.04	miod4184	2	0.02
miob3044	1Z	0.04	seoc2173	2	0.02
fcr4885	1Z	0.04	seoa6358	2	0.02
miob0178	1Z	0.04	fcr5222	2	0.02
seob1420	1Z	0.04	ncr4452	2	0.02
miob1493	1Z	0.04	mioc0347	2	0.02
seob9750	1Z	0.04	ncrc9483	2	0.02
fcrc2431	1Z	0.04	mioa2333	2	0.02
mioa9541	1Z	0.04	seoc4103	2	0.02
mioc8264	1Z	0.04	mioa1062	2	0.03
fcrb9588	2	9.42678e-04	ncrc4600	2	0.03
ncrc9280	2	1.36307e-03	seob1316	2	0.03
fcrc6826	2	1.61351e-03	seob1617	2	0.03
seoa1559	2	1.740315e-03	miod0884	2	0.03
ncrb8392	2	4.140103e-03	fcr1844	2	0.03
ncr4696	2	4.503228e-03	fcrb2160	2	0.03
ncrc9469	2	4.849487e-03	fcrc0604	2	0.03
fcrb9694	2	6.09468e-03	miob3456	2	0.03
ncr3559	2	7.002691e-03	miob4673	2	0.03
fcrb1950	2	7.501979e-03	miod1714	2	0.03
fcrb4925	2	7.651244e-03	fcrb6874	2	0.03
seoc2475	2	7.691468e-03	mioc7818	2	0.03
miod1505	2	8.44159e-03	mioa4057	2	0.03
seoa2391	2	9.669113e-03	fcrb9871	2	0.03
ncr0210	2	9.776908e-03	miob3928	2	0.03
fcrb9751	2	9.809161e-03	ncr3963	2	0.03
seob5773	2	0.01	miob3396	2	0.03
seoa1552	2	0.01	mioa1494	2	0.03
seoa1104	2	0.01	mioc1198	2	0.03
miob3354	2	0.01	miob4975	2	0.04
seob1793	2	0.01	mioa3629	2	0.04
seoc0951	2	0.01	fcr0665	2	0.04
seob3154	2	0.01	fcrb1382	2	0.04
mioc2619	2	0.01	mioa0890	2	0.04
seob7584	2	0.01	ncr3434	2	0.04
ncrb2395	2	0.01	hfcr3500	2	0.04
fcrb7070	2	0.01	fcrb1992	2	0.04
seob6413	2	0.01	mioa8774	2	0.04
ncrc1103	2	0.01	fcrb8208	2	0.04
seob5379	2	0.01	ncrc4226	2	0.04
seob1513	2	0.01	seob4147	2	0.04
hfcr3622	2	0.01	fcr0990	2	0.04
fcrc6563	2	0.01	fcrc7240	2	0.04
miob4055	2	0.02	fcr4460	2	0.04
seoa7509	2	0.02	miob3044	2	0.04
seoa6573	2	0.02	fcr4885	2	0.04
fcrb4696	2	0.02	miob0178	2	0.04
seob4805	2	0.02	seob1420	2	0.04
seoc1425	2	0.02	miob1493	2	0.04
mioc0630	2	0.02	seob9750	2	0.04
seob9614	2	0.02	fcrc2431	2	0.04
seob8501	2	0.02	mioa9541	2	0.04
miob2687	2	0.02	mioc8264	2	0.04
ncr3778	2	0.02	fcrb3217	4A	1.07e-08
mioa4014	2	0.02	fcr3053	4A	7.35e-08
seob3751	2	0.02	fcr3181	4A	7.35e-08
mioc0950	2	0.02	mioc3430	4A	2.08e-07
fcrb4542	2	0.02	seob5523	4A	7.14e-07
seoc1230	2	0.02	ncrb2092	4A	8.18e-07
fcrb8504	2	0.02	fcrb3227	4A	2.16e-06

mioa9473	4A	2.16e-06	hfcr3043	4A	3.19e-05
seob6853	4A	2.44e-06	miob3953	4A	3.41e-05
seob6576	4A	2.72e-06	mioa4014	4A	3.56e-05
ncr3163	4A	3.44e-06	mioc8423	4A	3.62e-05
fcrb2554	4A	3.76e-06	seob6844	4A	3.65e-05
seoc0775	4A	3.82e-06	mioc5532	4A	3.78e-05
seoa2970	4A	4.64e-06	miod1195	4A	3.78e-05
seob0085	4A	5.05e-06	miod5349	4A	3.78e-05
mioa2788	4A	5.98e-06	ncrc8903	4A	3.78e-05
mioa7317	4A	6.38e-06	fcr2607	4A	3.82e-05
seob3326	4A	6.84e-06	fcrb3654	4A	3.82e-05
fcr2952	4A	6.92e-06	ncr0045	4A	3.82e-05
seoc1203	4A	7.69e-06	ncrc5434	4A	3.82e-05
ncrc5243	4A	7.95e-06	seoa4717	4A	3.82e-05
fcrb4534	4A	8.04e-06	seoa9042	4A	3.82e-05
mioa3367	4A	8.23e-06	seob1911	4A	3.82e-05
fcrb3578	4A	8.3e-06	seob0154	4A	4.04e-05
miob6562	4A	8.53e-06	mioa0311	4A	4.07e-05
fcrc3993	4A	9.09e-06	miob6223	4A	4.11e-05
miod7414	4A	9.19e-06	ncrc6171	4A	4.13e-05
mioa9179	4A	9.26e-06	mioa2072	4A	4.19e-05
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seoa1427	4A	1.02e-05	seoa2585	4A	4.45e-05
miob6430	4A	1.1e-05	miod5123	4A	4.5e-05
fcr5075	4A	1.24e-05	seob0248	4A	4.5e-05
fcrb1892	4A	1.24e-05	seob6446	4A	4.81e-05
seoa8916	4A	1.24e-05	seoa4518	4A	5.34e-05
mioc7170	4A	1.26e-05	fcr6235	4A	5.39e-05
seob5240	4A	1.35e-05	hfcr1863	4A	5.39e-05
miob6419	4A	1.37e-05	hfcr3011	4A	5.39e-05
fcrc0487	4A	1.38e-05	mioa3939	4A	5.39e-05
seoa6133	4A	1.45e-05	mioa6130	4A	5.39e-05
mioc4022	4A	1.52e-05	ncr0258	4A	5.39e-05
mioa1585	4A	1.82e-05	ncr3197	4A	5.39e-05
cr0471	4A	1.83e-05	ncr3837	4A	5.39e-05
fcrb1960	4A	1.83e-05	fcrc2090	4A	5.47e-05
hfcr1137	4A	1.83e-05	seoc1593	4A	5.57e-05
hfcr8902	4A	1.83e-05	mioc8410	4A	5.58e-05
seoa0231	4A	1.83e-05	mioc7764	4A	5.6e-05
seoa8754	4A	1.83e-05	ncr0212	4A	5.86e-05
seob4427	4A	1.83e-05	seoc1023	4A	6.08e-05
seob2994	4A	1.84e-05	seob9282	4A	6.18e-05
mioa2319	4A	1.93e-05	fcr1463	4A	6.32e-05
seob6004	4A	2.07e-05	miod1236	4A	6.32e-05
fcr2103	4A	2.09e-05	seob0065	4A	6.32e-05
seoa4461	4A	2.14e-05	seob4029	4A	6.32e-05
mioa0595	4A	2.21e-05	fcrb8504	4A	6.63e-05
seob3518	4A	2.35e-05	seoc2029	4A	6.66e-05
fcrb6939	4A	2.39e-05	seoa3516	4A	7.05e-05
mioa3923	4A	2.39e-05	fcr4831	4A	7.47e-05
mioa5059	4A	2.39e-05	fcrc3739	4A	7.47e-05
ncrc9899	4A	2.47e-05	miod5369	4A	7.47e-05
ncr5568	4A	2.59e-05	ncr5168	4A	7.47e-05
mioa4636	4A	2.66e-05	miob1231	4A	7.53e-05
ncrb4441	4A	2.66e-05	ncr0898	4A	7.53e-05
seoa0959	4A	2.66e-05	seob3367	4A	7.53e-05
seoa1940	4A	2.66e-05	fcr5559	4A	7.65e-05
seob3189	4A	2.66e-05	fcrb6012	4A	7.67e-05
seob4303	4A	2.66e-05	seob8368	4A	7.81e-05
seob1231	4A	2.9e-05	seoa8566	4A	8.04e-05
hfcr5919	4A	2.96e-05	seob3191	4A	8.14e-05
fcr4477	4A	3.17e-05	fcrb8516	4A	8.38e-05
fcrc7388	4A	3.17e-05	mioa4009	4A	8.69e-05
miod5651	4A	3.17e-05	seob6279	4A	8.69e-05

fcr1756	4A	8.79e-05	mioc7686	4A	1.62e-04
fcrc0112	4A	8.79e-05	fcrb7693	4A	1.65e-04
fcrc3750	4A	8.79e-05	miod6238	4A	1.65e-04
seoa0288	4A	9.34e-05	seob4333	4A	1.65e-04
seoa2949	4A	9.47e-05	seob6206	4A	1.72e-04
fcrb3461	4A	9.48e-05	ncrc5844	4A	1.73e-04
mioa9510	4A	9.71e-05	seob0755	4A	1.75e-04
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ncr2013	4A	1.01e-04	fcr7043	4A	1.91e-04
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miod5505	4A	1.03e-04	ncr0733	4A	1.91e-04
seoa3533	4A	1.03e-04	ncrb8693	4A	1.91e-04
seob5748	4A	1.03e-04	ncrc4597	4A	1.91e-04
seob7432	4A	1.03e-04	seoa0486	4A	1.91e-04
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mioa3913	4A	1.04e-04	mioc6075	4A	1.92e-04
mioa5695	4A	1.04e-04	seob0122	4A	1.92e-04
ncr7813	4A	1.04e-04	seoa9373	4A	1.99e-04
seoa1102	4A	1.04e-04	mioa8647	4A	2.01e-04
seob2148	4A	1.04e-04	ncr0808	4A	2.02e-04
seob4669	4A	1.04e-04	seoa6497	4A	2.02e-04
ncr7904	4A	1.06e-04	seoa6598	4A	2.06e-04
miod6845	4A	1.08e-04	seob0308	4A	2.13e-04
seoa5662	4A	1.08e-04	seoa1598	4A	2.2e-04
mioc4667	4A	1.1e-04	fcr5720	4A	2.22e-04
mioc8057	4A	1.12e-04	seob5743	4A	2.22e-04
seob6368	4A	1.12e-04	fcr6044	4A	2.23e-04
ncr0025	4A	1.15e-04	hfcr3019	4A	2.23e-04
miod4759	4A	1.16e-04	miod4142	4A	2.23e-04
mioa6064	4A	1.17e-04	seob6670	4A	2.23e-04
fcrc6888	4A	1.21e-04	miob1326	4A	2.27e-04
mioa0535	4A	1.21e-04	seob3119	4A	2.29e-04
ncr0478	4A	1.21e-04	miob3348	4A	2.34e-04
mioa0252	4A	1.24e-04	mioc0950	4A	2.34e-04
seoa7530	4A	1.27e-04	seoa0032	4A	2.34e-04
fcrb8740	4A	1.34e-04	fcr6577	4A	2.43e-04
mioc6114	4A	1.36e-04	hfcr1163	4A	2.47e-04
miob6881	4A	1.37e-04	seob7465	4A	2.5e-04
mioa1193	4A	1.41e-04	fcr2088	4A	2.54e-04
ncr2293	4A	1.41e-04	hfcr5604	4A	2.54e-04
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seoa9537	4A	1.41e-04	ncrc1140	4A	2.54e-04
seob0376	4A	1.41e-04	ncrc6005	4A	2.54e-04
seob1318	4A	1.41e-04	seoa0221	4A	2.54e-04
seob3182	4A	1.41e-04	seoa7443	4A	2.54e-04
seob3923	4A	1.41e-04	seob1862	4A	2.54e-04
seob6835	4A	1.41e-04	seob6467	4A	2.54e-04
fcrb8080	4A	1.42e-04	seoa3717	4A	2.58e-04
ncrc0342	4A	1.42e-04	seob6272	4A	2.58e-04
seoa8232	4A	1.42e-04	fcrc2082	4A	2.59e-04
seoa9357	4A	1.43e-04	seob6751	4A	2.59e-04
seoc0999	4A	1.46e-04	seoc6169	4A	2.59e-04
seob6851	4A	1.47e-04	mioc7665	4A	2.77e-04
fcrb3134	4A	1.48e-04	mioa1662	4A	2.78e-04
seob6131	4A	1.5e-04	seoa9482	4A	2.78e-04
fcrb1733	4A	1.51e-04	seoa3105	4A	2.79e-04
ncrb0782	4A	1.51e-04	fcrb8668	4A	2.81e-04
seoa3847	4A	1.55e-04	fcr1879	4A	2.88e-04
mioa4552	4A	1.58e-04	seob4419	4A	2.9e-04



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ncrb8385	4A	3.0e-04
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mioa3963	4A	3.31e-04
mioa4076	4A	3.32e-04
seob8204	4A	3.32e-04
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seoa5090	4A	3.52e-04
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fcrc5516	4A	3.67e-04
mioa8852	4A	3.67e-04
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seoa6315	4A	3.67e-04
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fcr5758	4A	3.82e-04
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mioc6987	4A	4.23e-04
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fcrb6968	4A	4.27e-04
fcrc1216	4A	4.35e-04
seoa8399	4A	4.37e-04

ncrc6953	4A	4.38e-04
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fcrb2060	4A	4.4e-04
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seob1879	4A	4.4e-04
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seob2810	4A	4.4e-04
seob3313	4A	4.4e-04
seob3670	4A	4.4e-04
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seob4545	4A	4.4e-04
seob4579	4A	4.52e-04
miob3763	4A	4.56e-04
ncr0912	4A	4.57e-04
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fcrb8465	4A	4.58e-04
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seob6015	4A	4.63e-04
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mioc4332	4A	4.81e-04
seob9882	4A	4.82e-04
seob9552	4A	4.83e-04
fcr5123	4A	4.86e-04
seoc0924	4A	4.93e-04
mioa6854	4A	4.95e-04
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ncrb7292	4A	4.99e-04
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miob4475	4A	5.09e-04
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mioc3716	4A	5.17e-04
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mioc4641	4A	5.24e-04
fcr0955	4A	5.26e-04
mioc8379	4A	5.31e-04
ncr3782	4A	5.46e-04
mioa9891	4A	5.55e-04
miob2705	4A	5.57e-04
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mioa5692	4A	5.71e-04
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seob4050	4A	5.71e-04
seob4555	4A	5.71e-04
ncrc0174	4A	5.72e-04
seoa4053	4A	5.77e-04
seoc2264	4A	5.79e-04
mioa8970	4A	5.84e-04
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fcrb5537	4A	6.02e-04

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seoa8543	4A	6.02e-04	fcrc3240	4A	8.94e-04
seob6492	4A	6.02e-04	hfcr2287	4A	8.94e-04
fcrc4658	4A	6.2e-04	ncr2182	4A	8.98e-04
fcrb9720	4A	6.21e-04	fcrb1420	4A	9.14e-04
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ncr2486	4A	6.43e-04	seoa7647	4A	9.23e-04
mioa1520	4A	6.55e-04	seoa6620	4A	9.33e-04
seoa5933	4A	6.71e-04	fcrb6009	4A	9.38e-04
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fcrc3358	4A	6.88e-04	hfcr1697	4A	9.38e-04
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seob6189	4A	6.88e-04	mioa1097	4A	9.38e-04
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fcr0253	4A	6.95e-04	ncr1563	4A	9.38e-04
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miob5495	4A	7.35e-04	seob4621	4A	9.38e-04
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seob2936	4A	7.35e-04	fcr5470	4A	9.65e-04
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mioc4318	4A	7.51e-04	ncrc2888	4A	9.82e-04
fcrb2292	4A	7.53e-04	seob0304	4A	9.82e-04
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fcrc1849	4A	7.65e-04	ncrb6530	4A	9.9e-04
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fcr6937	4A	7.85e-04	seob3307	4A	1.019572e-03
fcrb2658	4A	7.85e-04	mioa9294	4A	1.023327e-03
mioa8946	4A	7.85e-04	ncrc8841	4A	1.026636e-03
miob2836	4A	7.85e-04	seoa0931	4A	1.029283e-03
mioc6947	4A	7.85e-04	fcrb1552	4A	1.033819e-03
seob2188	4A	7.85e-04	seoc3876	4A	1.036352e-03
seob2697	4A	7.85e-04	fcrc0241	4A	1.040278e-03
hfcr9613	4A	7.88e-04	seoa5577	4A	1.046877e-03
ncrc3464	4A	7.96e-04	miob5736	4A	1.05271e-03
mioa5085	4A	8.03e-04	seob9067	4A	1.059844e-03
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seoa8894	4A	1.153252e-03	mioa9935	4A	1.481624e-03
seob9145	4A	1.153252e-03	fcr2074	4A	1.495497e-03
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fcrc6854	4A	1.225922e-03	fcr6415	4A	1.65459e-03
seoa1856	4A	1.22754e-03	seoa6573	4A	1.659636e-03
mioa5468	4A	1.22757e-03	ncr4202	4A	1.662058e-03
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mioc6260	4A	1.462698e-03	fcr6016	4A	1.867933e-03
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seob2987	4A	1.867933e-03	seob1008	4A	2.317623e-03
seob4030	4A	1.867933e-03	seob1383	4A	2.317623e-03
seob4108	4A	1.867933e-03	seob3064	4A	2.317623e-03
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ncrb7329	4A	3.975596e-03	seob8300	4A	4.569266e-03
mioa0328	4A	4.030655e-03	fcrc1745	4A	4.587076e-03
seob0831	4A	4.04796e-03	seob0752	4A	4.588706e-03
fcrc5937	4A	4.057973e-03	mioa1626	4A	4.607822e-03
seob6133	4A	4.064124e-03	ncr7661	4A	4.609072e-03
miob3471	4A	4.066271e-03	fcrb3017	4A	4.625568e-03
fcrb5037	4A	4.068542e-03	fcrb3219	4A	4.625568e-03
mioc8434	4A	4.07859e-03	mioc1440	4A	4.625568e-03
fcrb6062	4A	4.105596e-03	ncr0438	4A	4.625568e-03
miob3426	4A	4.107551e-03	ncrc4798	4A	4.625568e-03
seoc3883	4A	4.107669e-03	seoa8979	4A	4.625568e-03
seob4117	4A	4.111207e-03	seoc2031	4A	4.625568e-03
miob5675	4A	4.125492e-03	seob0885	4A	4.636325e-03
fcrb3225	4A	4.150986e-03	miod1542	4A	4.642122e-03
fcrb7240	4A	4.155298e-03	fcrc6542	4A	4.660162e-03
fcrb9464	4A	4.155298e-03	mioc7561	4A	4.660162e-03
fcrc0379	4A	4.155298e-03	hfcr7855	4A	4.667117e-03
mioa6738	4A	4.155298e-03	seoa3863	4A	4.684362e-03
ncr0531	4A	4.155298e-03	miob9393	4A	4.704854e-03
seoa4783	4A	4.155298e-03	miob5708	4A	4.754388e-03
seoc2253	4A	4.155298e-03	miod2888	4A	4.817047e-03
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fcrc2613	4A	4.15673e-03	miod7440	4A	4.824649e-03
seob2259	4A	4.15777e-03	ncr8153	4A	4.833622e-03
fcrc6916	4A	4.157873e-03	hfcr4423	4A	4.854665e-03
mioc6274	4A	4.205108e-03	seoa5742	4A	4.870803e-03
seob6879	4A	4.22005e-03	fcr7042	4A	4.873697e-03
miob7109	4A	4.239511e-03	fcr4984	4A	4.887289e-03
fcrb8877	4A	4.261651e-03	fcrb5812	4A	4.900673e-03
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seoa6621	4A	4.26298e-03	miob9209	4A	4.905985e-03
fcr1833	4A	4.264609e-03	fcrb1731	4A	4.960118e-03
fcr3983	4A	4.264609e-03	miod5698	4A	5.055279e-03
fcrb2596	4A	4.264609e-03	seoc2226	4A	5.062218e-03
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miob8583	4A	5.11893e-03	mioc8479	4A	5.706928e-03
seoc2336	4A	5.122604e-03	miod7461	4A	5.706928e-03
fcrb2591	4A	5.141567e-03	ncr3527	4A	5.706928e-03
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seob2221	4A	5.141567e-03	seob1766	4A	5.706928e-03
mioc3958	4A	5.159834e-03	fcrc1660	4A	5.732649e-03
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seob7658	4A	5.165418e-03	mioa3342	4A	5.993081e-03
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seoa2141	4A	5.238547e-03	ncrb8665	4A	6.032318e-03
seob1197	4A	5.238547e-03	seob0466	4A	6.055754e-03
seoa4023	4A	5.272613e-03	fcr0824	4A	6.069793e-03
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seob1187	4A	5.307914e-03	miod2525	4A	6.144214e-03
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mioc0375	4A	5.32483e-03	hfcr2808	4A	6.206246e-03
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hfcr0731	4A	6.583534e-03	ncrb4339	4A	7.48001e-03
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fcrb4016	4A	8.407716e-03	fcr2939	4A	9.185386e-03
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miob5646	4A	8.522582e-03	fcr0999	4A	9.416219e-03
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mioa4636	4C	6.55e-05	mioa6130	4C	2.04e-04
cr0471	4C	6.77e-05	seoc2264	4C	2.1e-04
miob6430	4C	7.39e-05	fcr7587	4C	2.15e-04
seoa1940	4C	7.43e-05	fcrb2554	4C	2.2e-04
mioa3913	4C	7.5e-05	ncr0212	4C	2.21e-04
fcrb1892	4C	7.58e-05	ncr3197	4C	2.22e-04
seoa9042	4C	7.7e-05	fcr2607	4C	2.23e-04
seoa0032	4C	8.0e-05	hfcr3256	4C	2.23e-04
mioa2319	4C	8.18e-05	fcr4846	4C	2.28e-04
seob5240	4C	8.29e-05	fcrc1381	4C	2.28e-04
ncrc9899	4C	8.35e-05	miob0167	4C	2.32e-04
fcr5075	4C	8.62e-05	mioa0311	4C	2.33e-04
ncrb2092	4C	8.8e-05	seoc1175	4C	2.33e-04
hfcr8902	4C	8.84e-05	mioc4022	4C	2.34e-04
seoa9482	4C	9.27e-05	mioa8970	4C	2.35e-04
seob6004	4C	9.64e-05	seob0065	4C	2.35e-04
fcrb7339	4C	9.87e-05	seob1911	4C	2.39e-04
fcrb8516	4C	9.9e-05	mioa3939	4C	2.4e-04
hfcr3043	4C	1.0e-04	ncr0045	4C	2.44e-04
ncrc5434	4C	1.0e-04	seoc0999	4C	2.44e-04
fcr4477	4C	1.01e-04	fcrc0554	4C	2.48e-04
fcrc3739	4C	1.03e-04	seoc1203	4C	2.49e-04
fcrb6939	4C	1.04e-04	fcrc0075	4C	2.58e-04
hfcr5919	4C	1.04e-04	fcr6235	4C	2.6e-04
mioa3923	4C	1.12e-04	seoc4960	4C	2.65e-04
seob4427	4C	1.16e-04	miob6223	4C	2.67e-04
ncrb4441	4C	1.22e-04	seob4191	4C	2.69e-04
hfcr1137	4C	1.23e-04	mioc2726	4C	2.7e-04



miob8694	4C	2.87e-04	fcr4831	4C	5.97e-04
ncr0258	4C	2.89e-04	mioa0595	4C	6.04e-04
ncr4126	4C	2.91e-04	seob9145	4C	6.11e-04
mioc6260	4C	2.92e-04	mioa1662	4C	6.2e-04
fcrb6012	4C	3.0e-04	fcrc3750	4C	6.22e-04
seoa4053	4C	3.03e-04	seoa1102	4C	6.3e-04
seob6467	4C	3.03e-04	miod4759	4C	6.36e-04
fcrc0112	4C	3.06e-04	mioc7686	4C	6.41e-04
ncr0153	4C	3.07e-04	ncrb2266	4C	6.45e-04
ncr1631	4C	3.07e-04	seob6835	4C	6.58e-04
seoa4366	4C	3.08e-04	mioa2537	4C	6.62e-04
seoc6169	4C	3.11e-04	seoa3717	4C	6.62e-04
mioa1585	4C	3.13e-04	fcrc3009	4C	6.69e-04
hfcr3011	4C	3.15e-04	mioc8410	4C	6.98e-04
seoa5662	4C	3.21e-04	mioa6418	4C	7.09e-04
seoa0486	4C	3.23e-04	mioc0950	4C	7.19e-04
seoa2949	4C	3.29e-04	miod1925	4C	7.23e-04
fcrc0487	4C	3.31e-04	ncrc9910	4C	7.24e-04
ncr3837	4C	3.33e-04	seoa0221	4C	7.25e-04
mioa7317	4C	3.37e-04	mioc5532	4C	7.27e-04
hfcr1863	4C	3.39e-04	mioc4089	4C	7.46e-04
fcr2573	4C	3.43e-04	mioc7764	4C	7.57e-04
seob5743	4C	3.48e-04	seoa4681	4C	7.58e-04
mioa5695	4C	3.5e-04	seob6131	4C	7.61e-04
fcrb6968	4C	3.6e-04	seob3303	4C	7.67e-04
seob7584	4C	3.63e-04	mioa4552	4C	7.78e-04
ncrc0342	4C	3.76e-04	ncr8843	4C	7.83e-04
ncrc5417	4C	3.79e-04	seoa9537	4C	7.83e-04
seob3854	4C	3.91e-04	seob9574	4C	7.88e-04
seob6279	4C	3.96e-04	seob0308	4C	7.98e-04
fcrb8504	4C	3.99e-04	mioa1193	4C	8.04e-04
seob3367	4C	4.04e-04	seob1318	4C	8.04e-04
fcrb7830	4C	4.09e-04	hfcr6687	4C	8.17e-04
seob3182	4C	4.09e-04	fcrb1496	4C	8.19e-04
hfcr4489	4C	4.15e-04	miob8320	4C	8.21e-04
fcrb4428	4C	4.19e-04	seob0376	4C	8.21e-04
ncr0898	4C	4.21e-04	seoa8979	4C	8.23e-04
mioc8057	4C	4.39e-04	seoa9357	4C	8.24e-04
miob1231	4C	4.43e-04	ncrb0782	4C	8.27e-04
mioc2911	4C	4.49e-04	seob3923	4C	8.31e-04
fcr5559	4C	4.69e-04	ncr2293	4C	8.33e-04
seoa6497	4C	4.69e-04	seob0755	4C	8.35e-04
seoa6598	4C	4.73e-04	hfcr0478	4C	8.43e-04
fcr1463	4C	4.77e-04	ncr0733	4C	8.46e-04
fcr2103	4C	4.84e-04	hfcr5220	4C	8.48e-04
seob3191	4C	4.89e-04	ncrc5844	4C	8.48e-04
seob1319	4C	4.91e-04	mioa5355	4C	8.58e-04
miod6845	4C	4.99e-04	ncr8041	4C	8.61e-04
ncrc5663	4C	5.0e-04	fcr0824	4C	8.62e-04
seob6844	4C	5.04e-04	seob2994	4C	8.67e-04
mioa9510	4C	5.12e-04	seob3119	4C	8.73e-04
ncrc4597	4C	5.18e-04	fcrb8668	4C	8.75e-04
fcr3664	4C	5.26e-04	seob6206	4C	8.88e-04
seob4669	4C	5.33e-04	mioa6731	4C	8.9e-04
seob9282	4C	5.33e-04	fcrb2556	4C	8.98e-04
ncr7813	4C	5.48e-04	ncr5568	4C	9.0e-04
seoa7530	4C	5.56e-04	mioc4667	4C	9.01e-04
seob0248	4C	5.56e-04	mioa5696	4C	9.03e-04
seoa0288	4C	5.7e-04	hfcr1163	4C	9.1e-04
mioa6064	4C	5.71e-04	miob7156	4C	9.1e-04
seoc6703	4C	5.75e-04	ncr0808	4C	9.12e-04
miob9907	4C	5.82e-04	hfcr3019	4C	9.19e-04
ncrc8903	4C	5.88e-04	fcrc3048	4C	9.26e-04
seob2148	4C	5.88e-04	fcrb9454	4C	9.3e-04

seoa6315	4C	9.33e-04	miod1195	4C	1.431152e-03
fcrb9655	4C	9.37e-04	fcrb2484	4C	1.447281e-03
ncrc0715	4C	9.39e-04	mioc6987	4C	1.45158e-03
seoa8348	4C	9.56e-04	fcr1879	4C	1.452287e-03
fcrb9420	4C	9.64e-04	mioa6721	4C	1.457877e-03
seob6272	4C	9.74e-04	seob6486	4C	1.458125e-03
fcr2798	4C	9.78e-04	seoa3516	4C	1.46015e-03
seoc1996	4C	9.81e-04	ncr0025	4C	1.469905e-03
hfcr6486	4C	9.83e-04	hfcr1310	4C	1.478083e-03
ncrc9280	4C	1.0e-03	fcr3101	4C	1.487316e-03
seoa5090	4C	1.007122e-03	fcrb9959	4C	1.48762e-03
mioa2173	4C	1.00875e-03	fcrb5214	4C	1.490057e-03
ncrb5595	4C	1.013841e-03	ncrb4182	4C	1.50404e-03
fcrb2933	4C	1.016356e-03	ncrb3702	4C	1.511682e-03
fcr7043	4C	1.016688e-03	ncr7595	4C	1.511845e-03
miod1236	4C	1.028284e-03	mioa0577	4C	1.518616e-03
seob6446	4C	1.030592e-03	ncr8975	4C	1.524283e-03
seob2936	4C	1.039004e-03	seob4579	4C	1.527065e-03
ncrb8693	4C	1.046851e-03	fcr4128	4C	1.53383e-03
mioa9154	4C	1.070876e-03	ncrc5162	4C	1.553082e-03
seoa6658	4C	1.070876e-03	ncr5168	4C	1.55656e-03
ncrb2288	4C	1.076406e-03	ncrb3001	4C	1.557302e-03
fcrc7388	4C	1.081745e-03	fcrb8187	4C	1.573331e-03
fcrb9588	4C	1.089146e-03	ncrb4039	4C	1.584396e-03
miob8572	4C	1.097548e-03	miod1811	4C	1.590472e-03
seob8204	4C	1.099016e-03	seoa9740	4C	1.598061e-03
miob3982	4C	1.105438e-03	mioa3080	4C	1.603678e-03
ncrc0174	4C	1.123083e-03	hfcr3500	4C	1.610297e-03
miod5310	4C	1.129688e-03	mioa8852	4C	1.618546e-03
hfcr5604	4C	1.140826e-03	mioa0494	4C	1.619093e-03
seoa7443	4C	1.140826e-03	seoa0111	4C	1.622252e-03
fcrb1855	4C	1.142061e-03	ncr3782	4C	1.63287e-03
ncr3713	4C	1.150048e-03	ncrc5569	4C	1.637974e-03
fcrb9269	4C	1.150659e-03	mioc6075	4C	1.640004e-03
mioa3395	4C	1.154329e-03	seoa1118	4C	1.653668e-03
seob8368	4C	1.154981e-03	mioa4076	4C	1.665908e-03
seob0122	4C	1.171391e-03	seoa4305	4C	1.678116e-03
mioa0535	4C	1.173792e-03	fcrc6826	4C	1.682437e-03
miob1062	4C	1.177608e-03	mioa1015	4C	1.68644e-03
seob1793	4C	1.177608e-03	seob2185	4C	1.70771e-03
seoc1593	4C	1.178329e-03	fcrc2090	4C	1.719751e-03
miob9336	4C	1.178419e-03	seoa9870	4C	1.728369e-03
ncrc0090	4C	1.185916e-03	seob1414	4C	1.747109e-03
seob1862	4C	1.201035e-03	seoa9828	4C	1.753504e-03
seoa3105	4C	1.211669e-03	fcrb3165	4C	1.760242e-03
seob3670	4C	1.23222e-03	seoa1598	4C	1.770719e-03
hfcr6406	4C	1.239885e-03	fcrc2099	4C	1.790284e-03
miob4867	4C	1.256093e-03	seob1766	4C	1.794891e-03
ncrc1140	4C	1.256093e-03	hfcr1743	4C	1.798381e-03
fcr5720	4C	1.2614e-03	seob1908	4C	1.798381e-03
miod6238	4C	1.278208e-03	seob4545	4C	1.798381e-03
mioc7331	4C	1.301405e-03	fcrc5516	4C	1.799844e-03
ncrc6005	4C	1.305117e-03	hfcr5228	4C	1.800664e-03
miod1942	4C	1.305311e-03	mioa5692	4C	1.800664e-03
mioa0909	4C	1.312146e-03	seob4555	4C	1.800664e-03
seob1879	4C	1.347303e-03	fcrb1420	4C	1.801622e-03
miob6904	4C	1.355302e-03	fcr3595	4C	1.803204e-03
mioc2880	4C	1.356947e-03	ncr2666	4C	1.803204e-03
seob6368	4C	1.361315e-03	ncr2905	4C	1.815247e-03
ncr2472	4C	1.365497e-03	fcrb8940	4C	1.834572e-03
ncrb8385	4C	1.369106e-03	miob5495	4C	1.838333e-03
fcr1756	4C	1.392986e-03	ncr3368	4C	1.838333e-03
fcr2088	4C	1.408465e-03	fcrb1807	4C	1.859263e-03
miob3348	4C	1.428182e-03	ncrc5054	4C	1.860924e-03

seob6525	4C	1.861275e-03	seoa5577	4C	2.367648e-03
seoc0924	4C	1.861444e-03	seoa5235	4C	2.369839e-03
seoa8399	4C	1.88316e-03	ncrb8273	4C	2.393454e-03
fcrb8161	4C	1.885852e-03	fcrb3134	4C	2.402582e-03
mioa1520	4C	1.887743e-03	mioa9294	4C	2.412283e-03
fcrb8740	4C	1.892065e-03	hfcr1697	4C	2.435634e-03
seob2810	4C	1.901388e-03	ncrc5369	4C	2.435634e-03
fcr5758	4C	1.909224e-03	seob5219	4C	2.439695e-03
mioc8423	4C	1.916815e-03	mioc6114	4C	2.46067e-03
ncrc9729	4C	1.919544e-03	miob8143	4C	2.489145e-03
hfcr5695	4C	1.956159e-03	seoa1173	4C	2.502414e-03
seoc4380	4C	1.956915e-03	seoa3670	4C	2.543649e-03
fcrb2871	4C	1.964974e-03	miob0189	4C	2.57178e-03
mioc0592	4C	1.985622e-03	miob2705	4C	2.574869e-03
ncrc0150	4C	1.985831e-03	seoa8232	4C	2.578028e-03
fcrb2060	4C	1.99746e-03	fcr5123	4C	2.597097e-03
hfcr0415	4C	1.99746e-03	mioa6854	4C	2.602922e-03
seoa7555	4C	1.99746e-03	ncrc5061	4C	2.618499e-03
fcr2079	4C	2.016524e-03	seoc0369	4C	2.638551e-03
mioc0340	4C	2.021229e-03	fcr0139	4C	2.651872e-03
seoc1025	4C	2.02575e-03	fcr7004	4C	2.657357e-03
fcrb8080	4C	2.025786e-03	mioa9505	4C	2.658032e-03
mioc0824	4C	2.034483e-03	mioc8434	4C	2.661058e-03
seob0201	4C	2.050861e-03	seob7465	4C	2.711845e-03
fcrb9720	4C	2.057033e-03	fcrb4409	4C	2.722505e-03
fcr5470	4C	2.060807e-03	seoc0276	4C	2.725532e-03
ncrc4079	4C	2.066895e-03	fcr0999	4C	2.730498e-03
hfcr0624	4C	2.085152e-03	hfcr4488	4C	2.731117e-03
ncrb3329	4C	2.085152e-03	seoa0563	4C	2.731117e-03
seob6015	4C	2.09993e-03	fcr3559	4C	2.734761e-03
fcr4782	4C	2.115262e-03	mioa1660	4C	2.749542e-03
fcrb1733	4C	2.120875e-03	seoc0513	4C	2.753054e-03
fcrb9843	4C	2.120966e-03	ncrc9712	4C	2.760324e-03
ncr0238	4C	2.1386e-03	mioc5707	4C	2.770552e-03
mioc7895	4C	2.143605e-03	miob8711	4C	2.809832e-03
fcrb3718	4C	2.145161e-03	seob3307	4C	2.811695e-03
seob6670	4C	2.155534e-03	seob9946	4C	2.84126e-03
seob8501	4C	2.166556e-03	mioc7744	4C	2.845792e-03
mioc2525	4C	2.174809e-03	seoa8543	4C	2.874349e-03
mioc6312	4C	2.199817e-03	miob3898	4C	2.881671e-03
hfcr1733	4C	2.209362e-03	seoa8642	4C	2.881671e-03
ncrb4957	4C	2.210616e-03	mioa7140	4C	2.898369e-03
seob0089	4C	2.211811e-03	seoa7546	4C	2.919393e-03
hfcr6651	4C	2.216864e-03	fcr4763	4C	2.928101e-03
hfcr1302	4C	2.226095e-03	miob5016	4C	2.928675e-03
seob4050	4C	2.226095e-03	fcrc1849	4C	2.952953e-03
fcrb2536	4C	2.230106e-03	ncrc3464	4C	2.965232e-03
mioa8851	4C	2.23281e-03	fcrb3483	4C	2.983789e-03
fcr3121	4C	2.234303e-03	seob9649	4C	2.997767e-03
seoa2012	4C	2.255872e-03	seoa4600	4C	2.998627e-03
seoc1118	4C	2.258564e-03	seoa0008	4C	3.007551e-03
fcr7419	4C	2.260166e-03	seob0168	4C	3.016761e-03
seob7432	4C	2.272415e-03	seob2221	4C	3.044324e-03
mioc4318	4C	2.279552e-03	ncrc5079	4C	3.050155e-03
fcrc0695	4C	2.279562e-03	fcrb9481	4C	3.074875e-03
seoa8443	4C	2.285067e-03	ncrb0054	4C	3.127244e-03
fcrc6566	4C	2.298537e-03	seoa3533	4C	3.13784e-03
miob1326	4C	2.329343e-03	mioc5369	4C	3.159305e-03
miob4475	4C	2.330183e-03	seoa5683	4C	3.160612e-03
ncrc9469	4C	2.33257e-03	fcrb2218	4C	3.164316e-03
fcr0224	4C	2.334725e-03	mioa0407	4C	3.167049e-03
mioc6467	4C	2.34447e-03	fcrb7693	4C	3.203691e-03
seob4273	4C	2.355513e-03	seoa9160	4C	3.207335e-03
hfcr6700	4C	2.362015e-03	miob4836	4C	3.218792e-03

ncr0438	4C	3.245826e-03	seob3869	4C	4.093483e-03
ncrb6530	4C	3.252247e-03	seoa2641	4C	4.10684e-03
ncrc0100	4C	3.298912e-03	seoa6620	4C	4.118774e-03
ncrc2776	4C	3.322303e-03	mioc0741	4C	4.154883e-03
ncrb3942	4C	3.332792e-03	fcrb9694	4C	4.20251e-03
ncrb0513	4C	3.349517e-03	ncrc4531	4C	4.208322e-03
ncr1387	4C	3.356296e-03	ncrb7292	4C	4.220365e-03
ncrb0145	4C	3.359507e-03	miod4140	4C	4.240281e-03
fcrb3017	4C	3.376066e-03	hfcr0045	4C	4.261381e-03
ncrc5091	4C	3.385978e-03	ncrc9877	4C	4.26595e-03
fcrc0241	4C	3.422538e-03	seoc2191	4C	4.272909e-03
seob0514	4C	3.423122e-03	mioc3716	4C	4.281847e-03
ncr8866	4C	3.437719e-03	fcrb3725	4C	4.312352e-03
fcrc6888	4C	3.449333e-03	seoa9711	4C	4.329889e-03
miob9065	4C	3.456747e-03	ncrc9772	4C	4.399985e-03
seoa0549	4C	3.456908e-03	seoa6573	4C	4.452642e-03
mioa3514	4C	3.46245e-03	mioa0380	4C	4.489956e-03
ncr3237	4C	3.46245e-03	mioa1097	4C	4.509349e-03
ncrc4991	4C	3.4643e-03	seob3462	4C	4.509349e-03
seob3499	4C	3.4643e-03	mioa8811	4C	4.52055e-03
ncrc9855	4C	3.46879e-03	fcrc0959	4C	4.530274e-03
seoa1036	4C	3.477733e-03	seob3154	4C	4.531125e-03
miod6029	4C	3.517177e-03	mioa0890	4C	4.570501e-03
ncr2013	4C	3.51941e-03	fcrc6335	4C	4.58749e-03
seob4972	4C	3.531512e-03	ncrc5760	4C	4.601184e-03
hfcr0130	4C	3.533831e-03	mioa1354	4C	4.601629e-03
fcrb4378	4C	3.540302e-03	mioa1427	4C	4.633362e-03
mioc3726	4C	3.550472e-03	ncrc3840	4C	4.633362e-03
seob2188	4C	3.584274e-03	seoa0799	4C	4.633362e-03
seob1667	4C	3.640309e-03	seoa4040	4C	4.639931e-03
seoa6661	4C	3.644681e-03	miod4348	4C	4.655192e-03
seoa1720	4C	3.649977e-03	seoa7902	4C	4.66728e-03
seob2108	4C	3.666209e-03	seoa2978	4C	4.686163e-03
ncr0478	4C	3.666381e-03	ncrc5150	4C	4.691321e-03
fcrb2249	4C	3.695741e-03	ncr1563	4C	4.707547e-03
ncrb8134	4C	3.708615e-03	seob4621	4C	4.707547e-03
seob9750	4C	3.708927e-03	fcrc7047	4C	4.744327e-03
fcr6577	4C	3.735652e-03	seob5562	4C	4.746427e-03
hfcr0676	4C	3.735778e-03	ncrb4912	4C	4.752707e-03
miob2492	4C	3.735778e-03	mioa6739	4C	4.778158e-03
mioa1971	4C	3.738256e-03	seoa4395	4C	4.779169e-03
seob5954	4C	3.738256e-03	hfcr6468	4C	4.79651e-03
miob8932	4C	3.752087e-03	ncrb8253	4C	4.799003e-03
ncrc4808	4C	3.775334e-03	seoa5986	4C	4.799003e-03
mioa5085	4C	3.775842e-03	miob5736	4C	4.80808e-03
seoa4586	4C	3.780119e-03	seoa7517	4C	4.870405e-03
seoa3408	4C	3.790116e-03	mioa0826	4C	4.884238e-03
hfcr0370	4C	3.8121e-03	fcrb4415	4C	4.898061e-03
mioa8774	4C	3.812303e-03	mioa6621	4C	4.904983e-03
seob1187	4C	3.817075e-03	mioc1122	4C	4.93196e-03
fcr3155	4C	3.832262e-03	ncrc6795	4C	4.933324e-03
ncr2182	4C	3.847974e-03	seoa3847	4C	4.942903e-03
ncrc9557	4C	3.849741e-03	mioa9831	4C	4.946737e-03
miob0974	4C	3.874121e-03	fcr5625	4C	4.99519e-03
fcrb6009	4C	3.925377e-03	ncr3684	4C	5.017654e-03
mioc5643	4C	3.926872e-03	hfcr2287	4C	5.054567e-03
miod7243	4C	3.934025e-03	fcrc2576	4C	5.063792e-03
ncrc3434	4C	3.939813e-03	fcrc0430	4C	5.084925e-03
seob0200	4C	3.979023e-03	ncrc5672	4C	5.11611e-03
hfcr9613	4C	4.011004e-03	fcr6497	4C	5.124127e-03
miob4055	4C	4.011569e-03	mioa5468	4C	5.124127e-03
miob4956	4C	4.05244e-03	seoa6923	4C	5.124127e-03
miob0154	4C	4.08718e-03	miob0865	4C	5.128184e-03
seoa2442	4C	4.093483e-03	mioa8946	4C	5.185969e-03

fcr0056	4C	5.190905e-03	ncr4550	4C	6.099859e-03
ncrc5039	4C	5.197151e-03	mioc7444	4C	6.13308e-03
hfcr5009	4C	5.200779e-03	seoa3704	4C	6.146625e-03
miod2639	4C	5.218734e-03	hfcr1265	4C	6.161536e-03
fcrc4360	4C	5.250167e-03	seob0321	4C	6.178138e-03
fcrb4241	4C	5.25156e-03	fcrb7981	4C	6.206858e-03
fcrc6563	4C	5.282794e-03	seob3520	4C	6.215767e-03
seoa2122	4C	5.287317e-03	ncrc0101	4C	6.221193e-03
fcr0768	4C	5.301658e-03	ncrb6833	4C	6.229488e-03
miod3854	4C	5.307923e-03	ncr0075	4C	6.26855e-03
fcrc1745	4C	5.32716e-03	mioa8952	4C	6.270044e-03
mioa4196	4C	5.344108e-03	ncr0766	4C	6.276933e-03
mioc8619	4C	5.353299e-03	ncrc6817	4C	6.276933e-03
ncrc4654	4C	5.369673e-03	mioa2013	4C	6.287512e-03
seob4515	4C	5.369673e-03	seob9485	4C	6.301111e-03
ncr6232	4C	5.407943e-03	miod4142	4C	6.383134e-03
mioc2074	4C	5.414445e-03	miob4593	4C	6.402894e-03
ncrc9758	4C	5.427537e-03	fcr5779	4C	6.474618e-03
ncr4545	4C	5.438486e-03	seoa6197	4C	6.486591e-03
ncr9429	4C	5.458161e-03	seob0703	4C	6.50097e-03
fcrb8110	4C	5.478029e-03	miob6821	4C	6.505915e-03
seoa0029	4C	5.480759e-03	ncrb8343	4C	6.552284e-03
seob0031	4C	5.509288e-03	seoa5911	4C	6.597064e-03
mioc0222	4C	5.512684e-03	mioc2166	4C	6.609859e-03
seoa1856	4C	5.531453e-03	fcrb9352	4C	6.647947e-03
fcrc6854	4C	5.540234e-03	fcrb2292	4C	6.653984e-03
fcrc2082	4C	5.550695e-03	seob4039	4C	6.713668e-03
seob2987	4C	5.569207e-03	fcrb5422	4C	6.7264e-03
mioa1473	4C	5.580693e-03	ncrc2119	4C	6.756046e-03
fcrb9871	4C	5.592316e-03	seob9552	4C	6.762169e-03
seob4030	4C	5.594557e-03	fcrb3841	4C	6.780973e-03
mioa2158	4C	5.639619e-03	miob6988	4C	6.80749e-03
fcr4795	4C	5.649808e-03	hfcr1760	4C	6.835569e-03
seob5726	4C	5.65605e-03	hfcr5473	4C	6.857537e-03
fcrb7852	4C	5.667225e-03	fcrc3415	4C	6.861942e-03
ncrl1550	4C	5.713507e-03	hfcr5987	4C	6.867295e-03
mioa3471	4C	5.716154e-03	seoa0926	4C	6.867921e-03
mioa0132	4C	5.738039e-03	miob1115	4C	6.869801e-03
mioa8647	4C	5.768458e-03	fcr4380	4C	6.880921e-03
mioa1445	4C	5.811166e-03	miob5412	4C	6.89987e-03
seoc3588	4C	5.826485e-03	ncr6335	4C	6.907692e-03
ncrc3468	4C	5.832748e-03	seoa3628	4C	6.949533e-03
miob9052	4C	5.833135e-03	seob9772	4C	6.956817e-03
mioc5664	4C	5.835444e-03	mioa9581	4C	6.958796e-03
fcrb2137	4C	5.84394e-03	ncr2486	4C	6.982956e-03
hfcr5207	4C	5.84394e-03	miob0877	4C	6.983468e-03
mioa2327	4C	5.859459e-03	ncr0240	4C	6.999641e-03
fcrb9147	4C	5.861796e-03	seoa6137	4C	7.003723e-03
seob5458	4C	5.862878e-03	mioa1337	4C	7.012816e-03
seoa5554	4C	5.877316e-03	fcr6415	4C	7.029261e-03
fcrb5254	4C	5.890258e-03	seob1385	4C	7.029563e-03
seoa1552	4C	5.896449e-03	ncrb8207	4C	7.041692e-03
seoa3230	4C	5.898784e-03	hfcr1914	4C	7.057729e-03
fcr1844	4C	5.913324e-03	ncrl351	4C	7.095309e-03
fcrb5267	4C	5.942373e-03	seob2803	4C	7.108081e-03
fcrb6896	4C	5.949973e-03	seob5012	4C	7.108081e-03
seoa4524	4C	5.958281e-03	seob7474	4C	7.109226e-03
fcrc0094	4C	5.96467e-03	mioc7818	4C	7.166952e-03
miob3684	4C	5.971717e-03	mioa4241	4C	7.17269e-03
fcr6390	4C	6.000719e-03	seoa2136	4C	7.196923e-03
seob1737	4C	6.007946e-03	seoa9935	4C	7.197022e-03
fcr2074	4C	6.018802e-03	fcr5339	4C	7.199684e-03
seoc2131	4C	6.08684e-03	miob2836	4C	7.210691e-03
fcr0608	4C	6.096137e-03	mioa0104	4C	7.212787e-03

seob6413	4C	7.229514e-03	miob2855	4C	8.459946e-03
ncr3948	4C	7.237837e-03	seoa1263	4C	8.459946e-03
mioa6093	4C	7.268139e-03	seoa7459	4C	8.497761e-03
seoa1559	4C	7.27224e-03	seob2658	4C	8.497761e-03
hfcr9549	4C	7.295285e-03	ncrc6871	4C	8.532381e-03
seob1191	4C	7.325599e-03	seoa7474	4C	8.568552e-03
miob4058	4C	7.329008e-03	ncrc1502	4C	8.575665e-03
fcr5723	4C	7.369143e-03	fcrc2997	4C	8.587588e-03
mioa0328	4C	7.377639e-03	mioa9891	4C	8.689171e-03
seoc3993	4C	7.378389e-03	hfcr3928	4C	8.732239e-03
miod5703	4C	7.424044e-03	mioa2478	4C	8.749534e-03
fcr6044	4C	7.452917e-03	seoa7509	4C	8.755591e-03
seob6560	4C	7.500236e-03	mioa6738	4C	8.769774e-03
fcr6016	4C	7.53305e-03	seoa7178	4C	8.77984e-03
miod6162	4C	7.584327e-03	seob5319	4C	8.811962e-03
seoa2363	4C	7.617361e-03	fcrc0654	4C	8.812335e-03
seob2169	4C	7.634987e-03	miob1506	4C	8.830271e-03
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fcr6931	4C	7.680441e-03	seoa5547	4C	8.932311e-03
seoa6152	4C	7.680441e-03	seob3169	4C	8.97374e-03
fcr4622	4C	7.681578e-03	mioa3629	4C	8.97697e-03
mioa1324	4C	7.698039e-03	miob3696	4C	8.981708e-03
fcrb7944	4C	7.767483e-03	fcrc4054	4C	8.989376e-03
ncr1802	4C	7.784697e-03	mioa2413	4C	9.000025e-03
seob7729	4C	7.786058e-03	fcr2160	4C	9.030333e-03
seob2966	4C	7.806257e-03	ncr4539	4C	9.030333e-03
seob4108	4C	7.828518e-03	mioa0707	4C	9.037843e-03
ncr2484	4C	7.879438e-03	ncr3496	4C	9.054107e-03
ncrb3585	4C	7.879438e-03	ncrc0667	4C	9.054835e-03
seoa0913	4C	7.91186e-03	seob4807	4C	9.055692e-03
ncr0612	4C	7.925456e-03	ncrc9428	4C	9.100754e-03
mioc7998	4C	7.939586e-03	mioa2652	4C	9.114417e-03
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fcrb6768	4C	7.961352e-03	fcr0707	4C	9.142522e-03
seoa3245	4C	7.995448e-03	mioa9649	4C	9.154014e-03
miob7309	4C	8.045055e-03	miob3938	4C	9.20224e-03
hfcr5905	4C	8.045743e-03	seoa5933	4C	9.204501e-03
miob2227	4C	8.045772e-03	miob5675	4C	9.254824e-03
fcrb7113	4C	8.05715e-03	seoa2391	4C	9.263207e-03
hfcr6501	4C	8.058052e-03	fcrb6191	4C	9.290334e-03
ncrb1373	4C	8.093663e-03	ncrc0383	4C	9.294641e-03
fcrc0295	4C	8.130412e-03	miob4743	4C	9.329707e-03
mioa9717	4C	8.135586e-03	ncrb3284	4C	9.343469e-03
seob4209	4C	8.135586e-03	ncrc6953	4C	9.345199e-03
miod2665	4C	8.152135e-03	ncrc4757	4C	9.409517e-03
fcrc3358	4C	8.156756e-03	seob5032	4C	9.43118e-03
fcr4965	4C	8.164022e-03	ncrb6453	4C	9.583937e-03
mioc6997	4C	8.185087e-03	ncrc5553	4C	9.583937e-03
miob1493	4C	8.197903e-03	seob0418	4C	9.583937e-03
fcr0593	4C	8.19812e-03	seob0810	4C	9.583937e-03
fcr4129	4C	8.215271e-03	mioa4548	4C	9.611891e-03
ncr0912	4C	8.275646e-03	fcrc5846	4C	9.622113e-03
seob0466	4C	8.285506e-03	fcrb1503	4C	9.664889e-03
mioa9630	4C	8.304775e-03	ncrc1873	4C	9.678381e-03
ncrb6192	4C	8.312148e-03	ncrc0846	4C	9.679567e-03
seoc2824	4C	8.3183e-03	seob3064	4C	9.679567e-03
seoa0070	4C	8.335344e-03	seob5778	4C	9.689819e-03
seoa1736	4C	8.342294e-03	fcrb5537	4C	9.69729e-03
miob9848	4C	8.369066e-03	hfcr1419	4C	9.717051e-03
seoa1104	4C	8.378822e-03	mioa6035	4C	9.789009e-03
ncr0634	4C	8.421583e-03	seoa0003	4C	9.794242e-03
seoa5465	4C	8.437929e-03	seoc4416	4C	9.841173e-03
seob8065	4C	8.459463e-03	seob6492	4C	9.84478e-03

mioa8998	4C	9.861386e-03	fcrb8162	4C	0.01
ncrb1802	4C	9.861386e-03	fcrb3702	4C	0.01
seob8817	4C	9.894482e-03	seoa4017	4C	0.01
fcrb1578	4C	9.906745e-03	seob5441	4C	0.01
fcr2164	4C	9.970513e-03	mioa9792	4C	0.01
seoa4452	4C	9.989774e-03	mioa2536	4C	0.01
miob8214	4C	0.01	seoc3876	4C	0.01
miod2837	4C	0.01	hfcr5237	4C	0.01
mioc4366	4C	0.01	seoa6393	4C	0.01
fcr5354	4C	0.01	mioa9033	4C	0.01
fcr0955	4C	0.01	fcr3823	4C	0.01
fcrc3240	4C	0.01	ncrc0304	4C	0.01
fcr4699	4C	0.01	ncrb4390	4C	0.01
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seoa0511	4C	0.01	fcrc0350	4C	0.01
fcrb2713	4C	0.01	fcrb4570	4C	0.01
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ncrb1956	4C	0.01	hfcr6716	4C	0.01
fcrc5351	4C	0.01	mioc1609	4C	0.01
mioa2580	4C	0.01	ncrc0292	4C	0.01
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hfcr0829	4C	0.01	seob3007	4C	0.01
seob1574	4C	0.01	miod6731	4C	0.01
seoa8556	4C	0.01	fcrb7588	4C	0.01
mioa1285	4C	0.01	seoc2226	4C	0.01
seoa2162	4C	0.01	seob8693	4C	0.01
seob1383	4C	0.01	mioa4064	4C	0.01
hfcr6509	4C	0.01	fcrc0396	4C	0.01
ncrb0033	4C	0.01	ncrb4319	4C	0.01
miob4574	4C	0.01	miob9393	4C	0.01
fcr1337	4C	0.01	mioc3206	4C	0.01
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fcr2167	4C	0.01	ncrc8841	4C	0.01
mioa3812	4C	0.01	fcrc6990	4C	0.01
miob4037	4C	0.01	seob5927	4C	0.01
seoa9814	4C	0.01	mioa1626	4C	0.01
seob1008	4C	0.01	seoa7295	4C	0.01
seob6836	4C	0.01	fcrb1202	4C	0.01
ncr3402	4C	0.01	fcrc1689	4C	0.01
mioa4667	4C	0.01	mioa5773	4C	0.01
fcr1068	4C	0.01	seob9882	4C	0.01
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fcrb5527	4C	0.01	ncrc3529	4C	0.01
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ncrb8451	4C	0.01	seoa0172	4C	0.01
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fcrb4109	4C	0.01	seoa6344	4C	0.01
seoa4264	4C	0.01	ncrc5806	4C	0.01
fcrc2948	4C	0.01	seob0478	4C	0.01
mioc0121	4C	0.01	mioc4247	4C	0.01
miod7457	4C	0.01	fcrb3704	4C	0.01
hfcr2148	4C	0.01	mioa5691	4C	0.01
seob3887	4C	0.01	ncr4202	4C	0.01
ncrb6087	4C	0.01	fcrc1216	4C	0.01
seob1916	4C	0.01	seob6133	4C	0.01
fcrc5577	4C	0.01	hfcr1671	4C	0.01
fcrb2635	4C	0.01	hfcr6256	4C	0.01
ncrc0863	4C	0.01	fcr1633	4C	0.01
seob4122	4C	0.01	fcrb1741	4C	0.01
fcrb3135	4C	0.01	seoc3603	4C	0.01

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fcr2958	4C	0.01	fcrb7453	4C	0.01
seoa2428	4C	0.01	seoa9729	4C	0.01
seoa1056	4C	0.01	ncrc6617	4C	0.01
miob0496	4C	0.01	hfcr1795	4C	0.01
seob3731	4C	0.01	fcrb5588	4C	0.01
seoc2447	4C	0.01	fcrb6432	4C	0.01
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mioa7323	4C	0.01	fcr6881	4C	0.01
ncrb3936	4C	0.01	seoa3007	4C	0.01
mioc1198	4C	0.01	seoa2957	4C	0.01
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mioc2694	4C	0.01	hfcr7966	4C	0.01
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ncrb6432	4C	0.01	mioa4321	4C	0.01
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seob9645	4C	0.01	fcrb8119	4C	0.01
fcr4214	4C	0.01	fcrb2813	4C	0.01
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ncrc9217	4C	0.01	mioc6847	4C	0.01
mioa5097	4C	0.01	miob4793	4C	0.01
ncrb5197	4C	0.01	seoa8912	4C	0.01
ncrc9727	4C	0.01	fcrb8901	4C	0.01
seoa2639	4C	0.01	seob4896	4C	0.01
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fcrb3244	4C	0.01	seob4766	4C	0.01
seoa0931	4C	0.01	ncrb6661	4C	0.01
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miob0361	4C	0.03
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mioa9007	4C	0.04	ncrb4538	4C	0.04
seoa2041	4C	0.04	hfcr5383	4C	0.04
seob3751	4C	0.04	miod2412	4C	0.04
hfcr1202	4C	0.04	fcrb5449	4C	0.04
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seob3734	4C	0.04	ncrc4000	4C	0.04
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fcrc0559	4C	0.04	mioa8314	4C	0.04
miob3131	4C	0.04	mioa7299	4C	0.04
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ncr3614	4C	0.04	miod7440	4E	2.44e-07
seob0497	4C	0.04	seoc2029	4E	6.23e-07
hfcr0675	4C	0.04	mioc7170	4E	2.53e-06
miob3443	4C	0.04	mioc2561	4E	3.17e-06
fcrb1724	4C	0.04	mioa2072	4E	3.26e-06
seob1748	4C	0.04	seob5523	4E	4.23e-06
seob1420	4C	0.04	seob4419	4E	4.27e-06
hfcr6931	4C	0.04	fcrc3993	4E	4.37e-06
seoc5285	4C	0.04	seoa4461	4E	5.29e-06
seob9543	4C	0.04	seoa6032	4E	5.48e-06
fcr4832	4C	0.04	miod5349	4E	6.31e-06
mioa3786	4C	0.04	mioc3430	4E	7.49e-06
mioc3618	4C	0.04	seoa8894	4E	1.1e-05
seob6582	4C	0.04	fcrb4534	4E	1.46e-05
fcr6412	4C	0.04	seob2697	4E	1.66e-05
miob9121	4C	0.04	seoa4518	4E	2.47e-05
fcrc4948	4C	0.04	seoa6133	4E	2.48e-05
ncr2304	4C	0.04	miob6562	4E	2.52e-05
seoa3335	4C	0.04	seoa8566	4E	3.22e-05
fcr4057	4C	0.04	ncr7668	4E	4.63e-05
seob1746	4C	0.04	fcrb3578	4E	4.7e-05
seob4213	4C	0.04	fcr2952	4E	5.1e-05
ncrc4247	4C	0.04	miod5123	4E	5.49e-05
seoa6697	4C	0.04	seob4333	4E	5.73e-05

seob6853	4E	5.74e-05	fcrb8504	4E	3.99e-04
mioa3963	4E	6.04e-05	fcr5779	4E	4.02e-04
miod7421	4E	6.08e-05	miob7922	4E	4.07e-04
mioa2327	4E	6.21e-05	fcrb7830	4E	4.09e-04
seoa9373	4E	6.54e-05	fcrb4428	4E	4.19e-04
mioa2319	4E	8.18e-05	mioc8057	4E	4.39e-04
ncrb2092	4E	8.8e-05	fcr1463	4E	4.77e-04
mioa1370	4E	8.87e-05	fcr2103	4E	4.84e-04
mioc8410	4E	9.18e-05	miod6845	4E	4.99e-04
seoa9482	4E	9.27e-05	ncrc5663	4E	5.0e-04
mioa3492	4E	9.61e-05	seob6844	4E	5.04e-04
fcrb7339	4E	9.87e-05	ncrc4597	4E	5.18e-04
fcrb8516	4E	9.9e-05	ncrc4757	4E	5.23e-04
fcr4477	4E	1.01e-04	seob9282	4E	5.33e-04
fcrc3739	4E	1.03e-04	seoa7530	4E	5.56e-04
fcrb0265	4E	1.2e-04	seob0248	4E	5.56e-04
seob6576	4E	1.27e-04	seoc6703	4E	5.75e-04
seob6189	4E	1.32e-04	miob9907	4E	5.82e-04
mioa5085	4E	1.33e-04	fcr2607	4E	5.84e-04
miod7414	4E	1.36e-04	ncrc8903	4E	5.88e-04
mioc2094	4E	1.38e-04	seoa4739	4E	5.91e-04
seoa1427	4E	1.38e-04	fcr4831	4E	5.97e-04
seoa2585	4E	1.47e-04	mioa0595	4E	6.04e-04
fcrb2536	4E	1.53e-04	seob9145	4E	6.11e-04
seob6851	4E	1.55e-04	mioa1662	4E	6.2e-04
fcrb5850	4E	1.56e-04	fcrc3750	4E	6.22e-04
miob8812	4E	1.56e-04	miod4759	4E	6.36e-04
fcrb3461	4E	1.6e-04	fcrc6826	4E	6.39e-04
seoc1023	4E	1.66e-04	mioc7686	4E	6.41e-04
seob4029	4E	1.69e-04	ncrb2266	4E	6.45e-04
seoa0536	4E	1.71e-04	ncrc1049	4E	6.5e-04
miod5651	4E	1.77e-04	ncrc3453	4E	6.5e-04
seoa2970	4E	1.77e-04	fcr2573	4E	6.62e-04
seob5748	4E	1.79e-04	mioa2537	4E	6.62e-04
miod5505	4E	1.89e-04	fcrc3009	4E	6.69e-04
seob6751	4E	2.02e-04	mioa6418	4E	7.09e-04
seoc2264	4E	2.1e-04	mioc0950	4E	7.19e-04
fcrb2554	4E	2.2e-04	miod1925	4E	7.23e-04
fcrc1381	4E	2.28e-04	mioc5532	4E	7.27e-04
miob0167	4E	2.32e-04	mioc4089	4E	7.46e-04
mioc4022	4E	2.34e-04	mioc7362	4E	7.52e-04
seob0065	4E	2.35e-04	mioc7764	4E	7.57e-04
fcrc5937	4E	2.36e-04	seob9960	4E	7.63e-04
seoc0999	4E	2.44e-04	seoa8388	4E	7.64e-04
fcrc0554	4E	2.48e-04	fcrc6976	4E	7.65e-04
seoc1203	4E	2.49e-04	seob3303	4E	7.67e-04
hfcr1073	4E	2.54e-04	ncr0853	4E	7.96e-04
seob4191	4E	2.69e-04	fcrb1496	4E	8.19e-04
mioc2726	4E	2.7e-04	seoa8979	4E	8.23e-04
miob8694	4E	2.87e-04	ncrc2080	4E	8.53e-04
mioc6260	4E	2.92e-04	mioa5355	4E	8.58e-04
seoa4053	4E	3.03e-04	ncr8041	4E	8.61e-04
fcrc0112	4E	3.06e-04	seob2994	4E	8.67e-04
ncr0153	4E	3.07e-04	fcrb8668	4E	8.75e-04
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seoa4366	4E	3.08e-04	fcrc7102	4E	8.87e-04
seoc6169	4E	3.11e-04	mioa6731	4E	8.9e-04
mioa1585	4E	3.13e-04	ncr5568	4E	9.0e-04
seoa2949	4E	3.29e-04	mioc4667	4E	9.01e-04
fcrc0487	4E	3.31e-04	ncr0808	4E	9.12e-04
mioa7317	4E	3.37e-04	hfcr3019	4E	9.19e-04
seob5743	4E	3.48e-04	fcrc3048	4E	9.26e-04
seob7584	4E	3.63e-04	fcrb9454	4E	9.3e-04
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seoc1996	4E	9.81e-04	ncr2905	4E	1.815247e-03
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seob6446	4E	1.030592e-03	fcrb8740	4E	1.892065e-03
miob7105	4E	1.073216e-03	mioc8423	4E	1.916815e-03
fcrc7388	4E	1.081745e-03	ncrc9729	4E	1.919544e-03
miob3982	4E	1.105438e-03	fcrb2871	4E	1.964974e-03
seoa0740	4E	1.112372e-03	miod0592	4E	1.985622e-03
fcrb1855	4E	1.142061e-03	ncrc0150	4E	1.985831e-03
fcrb9269	4E	1.150659e-03	miod5894	4E	2.014527e-03
mioa3395	4E	1.154329e-03	miod0340	4E	2.021229e-03
seob8368	4E	1.154981e-03	seob4560	4E	2.021887e-03
seob0122	4E	1.171391e-03	fcrb8080	4E	2.025786e-03
mioa0535	4E	1.173792e-03	mioc0824	4E	2.034483e-03
fcrb1539	4E	1.177578e-03	ncrb8330	4E	2.048755e-03
seoc1593	4E	1.178329e-03	fcrb5675	4E	2.051294e-03
miob9336	4E	1.178419e-03	mioa8899	4E	2.051294e-03
seob3191	4E	1.178567e-03	fcrb9720	4E	2.057033e-03
ncrc0090	4E	1.185916e-03	mioc1107	4E	2.070013e-03
miod6238	4E	1.278208e-03	miob9163	4E	2.097664e-03
miod1942	4E	1.305311e-03	miob5432	4E	2.108077e-03
ncr4539	4E	1.309997e-03	fcrb1733	4E	2.120875e-03
mioa0909	4E	1.312146e-03	fcrb9843	4E	2.120966e-03
seoa1844	4E	1.345317e-03	fcrc6916	4E	2.121527e-03
mioc2880	4E	1.356947e-03	ncr0238	4E	2.1386e-03
seob6368	4E	1.361315e-03	mioa3598	4E	2.13862e-03
mioc2348	4E	1.386736e-03	mioc7895	4E	2.143605e-03
fcr1756	4E	1.392986e-03	seob6670	4E	2.155534e-03
miod6038	4E	1.395436e-03	seob8501	4E	2.166556e-03
miod0080	4E	1.423952e-03	miod2525	4E	2.174809e-03
miob3348	4E	1.428182e-03	fcrb2624	4E	2.174826e-03
miod1195	4E	1.431152e-03	fcrb6187	4E	2.177878e-03
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mioc6987	4E	1.45158e-03	seoc1906	4E	2.1992e-03
seoa3516	4E	1.46015e-03	mioc6312	4E	2.199817e-03
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fcr4128	4E	1.53383e-03	seob7432	4E	2.272415e-03
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ncr5168	4E	1.55656e-03	seoa1065	4E	2.312579e-03
fcrb8187	4E	1.573331e-03	fcrc6016	4E	2.3165e-03
miod1811	4E	1.590472e-03	miob1326	4E	2.329343e-03
seoa9740	4E	1.598061e-03	miob4475	4E	2.330183e-03
mioa3080	4E	1.603678e-03	fcrb3134	4E	2.402582e-03
mioc0052	4E	1.624699e-03	ncrb5254	4E	2.446454e-03
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mioc6075	4E	1.640004e-03	seoa3670	4E	2.543649e-03
seob0376	4E	1.666731e-03	seoa8232	4E	2.578028e-03
seoa4305	4E	1.678116e-03	ncrc1578	4E	2.579378e-03
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seob0304	4E	1.693307e-03	ncrc5061	4E	2.618499e-03
fcrc2090	4E	1.719751e-03	seoc1402	4E	2.660096e-03
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seoa1598	4E	1.770719e-03	seob7465	4E	2.711845e-03
fcrc2099	4E	1.790284e-03	fcrb4409	4E	2.722505e-03
seob1766	4E	1.794891e-03	seoc0276	4E	2.725532e-03
fcrc5516	4E	1.799844e-03	mioa1660	4E	2.749542e-03
fcrb1420	4E	1.801622e-03	seob3307	4E	2.811695e-03



mioc3962	4E	2.824707e-03	seoc3515	4E	4.159057e-03
seoa9814	4E	2.836239e-03	seoa8844	4E	4.195788e-03
seob9946	4E	2.84126e-03	ncrb7292	4E	4.220365e-03
seob4545	4E	2.842281e-03	fcrb9649	4E	4.270145e-03
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fcrb4391	4E	2.852331e-03	mioc3716	4E	4.281847e-03
fcr0224	4E	2.870823e-03	seoa9711	4E	4.329889e-03
seoa7478	4E	2.876929e-03	fcrb8467	4E	4.415815e-03
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mioa7140	4E	2.898369e-03	seoa6573	4E	4.452642e-03
ncrc6359	4E	2.898846e-03	seob0168	4E	4.459519e-03
seoc3854	4E	2.908161e-03	fcrc0959	4E	4.530274e-03
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mioa0702	4E	2.977964e-03	mioa1354	4E	4.601629e-03
seob9649	4E	2.997767e-03	fcrb2318	4E	4.630688e-03
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fcrb9481	4E	3.074875e-03	fcrb7931	4E	4.703478e-03
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ncrb0054	4E	3.127244e-03	seob5562	4E	4.746427e-03
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mioa2185	4E	3.147097e-03	mioa2691	4E	4.758155e-03
mioa0407	4E	3.167049e-03	ncr3369	4E	4.770221e-03
fcrb7693	4E	3.203691e-03	mioa6739	4E	4.778158e-03
fcrb1552	4E	3.209013e-03	seoa4395	4E	4.779169e-03
ncr0438	4E	3.245826e-03	mioa0826	4E	4.884238e-03
ncrb6530	4E	3.252247e-03	mioa6621	4E	4.904983e-03
mioa0187	4E	3.279663e-03	fcrb5438	4E	4.92339e-03
fcrc3211	4E	3.326366e-03	seoa3847	4E	4.942903e-03
fcr5075	4E	3.353508e-03	mioa9831	4E	4.946737e-03
ncrb0145	4E	3.359507e-03	fcrc6174	4E	4.953862e-03
fcrb3017	4E	3.376066e-03	fcrb3192	4E	4.985296e-03
ncr8866	4E	3.437719e-03	ncr3684	4E	5.017654e-03
mioc7441	4E	3.437924e-03	hfcr2287	4E	5.054567e-03
ncrc7040	4E	3.438068e-03	seob1318	4E	5.055898e-03
seoc7104	4E	3.438068e-03	fcrc2576	4E	5.063792e-03
fcrc6888	4E	3.449333e-03	fcrc0430	4E	5.084925e-03
miob9065	4E	3.456747e-03	miob8583	4E	5.097523e-03
fcrb2307	4E	3.463155e-03	ncrc5672	4E	5.11611e-03
miob7290	4E	3.492188e-03	ncr2862	4E	5.163569e-03
ncr2013	4E	3.51941e-03	miob6364	4E	5.172374e-03
seob4972	4E	3.531512e-03	ncrc5500	4E	5.175143e-03
mioc3726	4E	3.550472e-03	seob3204	4E	5.176722e-03
seob2188	4E	3.584274e-03	mioa8946	4E	5.185969e-03
seob2797	4E	3.6022e-03	ncrc5039	4E	5.197151e-03
seoa1749	4E	3.637644e-03	miod2639	4E	5.218734e-03
seoa6661	4E	3.644681e-03	fcrc4360	4E	5.250167e-03
ncr0478	4E	3.666381e-03	miod3592	4E	5.253602e-03
fcrb2249	4E	3.695741e-03	ncrb1398	4E	5.295501e-03
ncr0451	4E	3.707725e-03	miod3854	4E	5.307923e-03
fcr6577	4E	3.735652e-03	miod3254	4E	5.326719e-03
fcr6018	4E	3.762242e-03	mioc8619	4E	5.353299e-03
ncrc4808	4E	3.775334e-03	ncrc9758	4E	5.427537e-03
hfcr0370	4E	3.8121e-03	fcrb8110	4E	5.478029e-03
seob1187	4E	3.817075e-03	fcr0990	4E	5.490991e-03
fcr3155	4E	3.832262e-03	fcrb1684	4E	5.495549e-03
ncr2182	4E	3.847974e-03	fcrb6650	4E	5.525357e-03
mioc5643	4E	3.926872e-03	fcrc6854	4E	5.540234e-03
mioc7084	4E	3.93591e-03	ncrd1382	4E	5.540547e-03
seoa1173	4E	3.950326e-03	fcrc2082	4E	5.550695e-03
ncrb4025	4E	4.052138e-03	mioc3296	4E	5.567015e-03
miob4956	4E	4.05244e-03	fcrb7852	4E	5.667225e-03
miod6018	4E	4.139368e-03	fcr0253	4E	5.72015e-03
mioc0741	4E	4.154883e-03	mioa8647	4E	5.768458e-03

fcrb5164	4E	5.814619e-03	hfcr0517	4E	7.704251e-03
seoc3588	4E	5.826485e-03	fcrb7944	4E	7.767483e-03
mioc5664	4E	5.835444e-03	fcrb9655	4E	7.792172e-03
fcrb9147	4E	5.861796e-03	ncrc4226	4E	7.824984e-03
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fcrb5267	4E	5.942373e-03	ncrb1670	4E	7.921435e-03
fcrb1687	4E	5.960627e-03	mioc7998	4E	7.939586e-03
fcrc0094	4E	5.96467e-03	seob2775	4E	7.953567e-03
fcr6390	4E	6.000719e-03	miob2227	4E	8.045772e-03
seoa0470	4E	6.100317e-03	fcrb7113	4E	8.05715e-03
ncr3827	4E	6.109319e-03	fcrc0295	4E	8.130412e-03
hfcr1265	4E	6.161536e-03	miod2665	4E	8.152135e-03
fcrb7529	4E	6.171216e-03	fcrc3358	4E	8.156756e-03
seob3520	4E	6.215767e-03	fcr4965	4E	8.164022e-03
ncrb1337	4E	6.21911e-03	mioc6997	4E	8.185087e-03
ncrb1515	4E	6.341156e-03	miob1493	4E	8.197903e-03
miod4142	4E	6.383134e-03	seoc2220	4E	8.240295e-03
miob4593	4E	6.402894e-03	ncrb3077	4E	8.265993e-03
ncrc6712	4E	6.41394e-03	ncr0912	4E	8.275646e-03
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mioa5836	4E	6.490511e-03	seoc2824	4E	8.3183e-03
mioc0301	4E	6.490511e-03	hfcr5737	4E	8.332211e-03
ncr5719	4E	6.490511e-03	seoa4070	4E	8.351138e-03
seoa5473	4E	6.490511e-03	ncr0634	4E	8.421583e-03
seod2243	4E	6.490511e-03	seob8065	4E	8.459463e-03
seob0703	4E	6.50097e-03	ncrc6871	4E	8.532381e-03
seoa5911	4E	6.597064e-03	ncrc1502	4E	8.575665e-03
mioc2166	4E	6.609859e-03	fcrc2997	4E	8.587588e-03
ncr4545	4E	6.618737e-03	fcr0770	4E	8.634112e-03
seoa4333	4E	6.629988e-03	mioa3856	4E	8.663706e-03
mioa1303	4E	6.633139e-03	mioa9891	4E	8.689171e-03
fcrb2292	4E	6.653984e-03	fcrb1835	4E	8.733177e-03
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seob9552	4E	6.762169e-03	fcrc1834	4E	8.876728e-03
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hfcr1760	4E	6.835569e-03	fcrc4054	4E	8.989376e-03
fcrc3415	4E	6.861942e-03	mioa2413	4E	9.000025e-03
miob5412	4E	6.89987e-03	fcrb2299	4E	9.0502e-03
seob9772	4E	6.956817e-03	seob3415	4E	9.05062e-03
ncrc2495	4E	6.966429e-03	mioa2652	4E	9.114417e-03
ncr2486	4E	6.982956e-03	miob3461	4E	9.117224e-03
mioa1337	4E	7.012816e-03	fcr0707	4E	9.142522e-03
ncrc6813	4E	7.043646e-03	miod1574	4E	9.196145e-03
hfcr1914	4E	7.057729e-03	seoa5933	4E	9.204501e-03
mioa1427	4E	7.073426e-03	seoa2391	4E	9.263207e-03
ncr1351	4E	7.095309e-03	fcrb6191	4E	9.290334e-03
seoa6923	4E	7.09741e-03	ncrc0101	4E	9.315893e-03
seob7474	4E	7.109226e-03	ncrc6953	4E	9.345199e-03
mioa0249	4E	7.184179e-03	seoc0098	4E	9.429093e-03
seoa9935	4E	7.197022e-03	seob5032	4E	9.43118e-03
miob2836	4E	7.210691e-03	seoc1234	4E	9.440983e-03
mioa6093	4E	7.268139e-03	mioa4548	4E	9.611891e-03
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ncrc0769	4E	7.328795e-03	seob4140	4E	9.654697e-03
miob4058	4E	7.329008e-03	fcrb5537	4E	9.69729e-03
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fcr6044	4E	7.452917e-03	mioa6035	4E	9.789009e-03
seob6560	4E	7.500236e-03	fcrb3466	4E	9.829055e-03
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ncrc5972	4E	7.541349e-03	ncrc7038	4E	9.905278e-03
miob4221	4E	7.572537e-03	miob8214	4E	0.01
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fcrb1787	4E	0.01	seob3189	4E	0.01
mioa2580	4E	0.01	miob4743	4E	0.01
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seob3887	4E	0.01	ncr6142	4E	0.01
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seob2081	4E	0.01
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fcrc5142	4G	2.464685e-03	seoa6573	4G	3.875968e-03
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seoa3670	4G	2.543649e-03	ncrc3434	4G	3.939813e-03
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fcrb4409	4G	2.722505e-03	ncrc5492	4G	4.081573e-03
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mioa1660	4G	2.749542e-03	seoc3515	4G	4.159057e-03
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miob8146	4G	2.888517e-03	seoc2191	4G	4.272909e-03
mioa7140	4G	2.898369e-03	mioc0567	4G	4.279318e-03
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fcrb3872	4G	2.952114e-03	fcrb8467	4G	4.415815e-03
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fcrb9481	4G	3.074875e-03	fcr5681	4G	4.429139e-03
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seoa3533	4G	3.13784e-03	fcrc6335	4G	4.58749e-03
mioa2185	4G	3.147097e-03	mioa1354	4G	4.601629e-03
mioa3856	4G	3.151528e-03	miod4348	4G	4.655192e-03
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mioa0407	4G	3.167049e-03	ncrc5150	4G	4.691321e-03
fcrb7693	4G	3.203691e-03	seob5562	4G	4.746427e-03
fcrb1552	4G	3.209013e-03	ncrb4912	4G	4.752707e-03
ncrc6423	4G	3.223469e-03	fcr0707	4G	4.772856e-03
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fcr5075	4G	3.353508e-03	mioa6621	4G	4.904983e-03
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fcrb3017	4G	3.376066e-03	seoa5235	4G	4.928397e-03
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miod3854	4G	5.307923e-03	ncr9956	4G	6.920421e-03
miod3254	4G	5.326719e-03	seob9772	4G	6.956817e-03
mioc8619	4G	5.353299e-03	ncr2486	4G	6.982956e-03
ncrc0508	4G	5.409373e-03	mioa1337	4G	7.012816e-03
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fcrc6560	4G	5.571911e-03	ncr1351	4G	7.095309e-03
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hfcr0724	4G	5.834821e-03	seob1191	4G	7.325599e-03
mioc5664	4G	5.835444e-03	miob4058	4G	7.329008e-03
fcrb9147	4G	5.861796e-03	fcr5723	4G	7.369143e-03
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fcr1185	4G	5.966352e-03	mioa4009	4G	7.528646e-03
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fcr0608	4G	6.096137e-03	seob6177	4G	7.843092e-03
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miob6223	4I	2.67e-04	fcr4831	4I	5.97e-04
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ncr0258	4I	2.89e-04	seob9145	4I	6.11e-04
ncr4126	4I	2.91e-04	mioa1662	4I	6.2e-04
mioc6260	4I	2.92e-04	fcrc3750	4I	6.22e-04
fcrb6012	4I	3.0e-04	seoa1102	4I	6.3e-04

miod4759	4I	6.36e-04	seob6272	4I	9.74e-04
fcrc6826	4I	6.39e-04	seoa5090	4I	1.007122e-03
mioc7686	4I	6.41e-04	mioa2173	4I	1.00875e-03
ncrb2266	4I	6.45e-04	fcrc7240	4I	1.015969e-03
seob6835	4I	6.58e-04	fcrc7043	4I	1.016688e-03
mioa2537	4I	6.62e-04	miod1236	4I	1.028284e-03
seoa3717	4I	6.62e-04	seob6446	4I	1.030592e-03
fcrc3009	4I	6.69e-04	seob2936	4I	1.039004e-03
mioc8410	4I	6.98e-04	ncrb8693	4I	1.046851e-03
mioa6418	4I	7.09e-04	mioa9154	4I	1.070876e-03
mioc0950	4I	7.19e-04	seoa6658	4I	1.070876e-03
miod1925	4I	7.23e-04	ncrb2288	4I	1.076406e-03
ncrc9910	4I	7.24e-04	fcrc7388	4I	1.081745e-03
seoa0221	4I	7.25e-04	fcrc9588	4I	1.089146e-03
mioc5532	4I	7.27e-04	miob8572	4I	1.097548e-03
mioc4089	4I	7.46e-04	seob8204	4I	1.099016e-03
mioc7764	4I	7.57e-04	miod5894	4I	1.100493e-03
seoa4681	4I	7.58e-04	ncrc0174	4I	1.123083e-03
seob6131	4I	7.61e-04	hfcr5604	4I	1.140826e-03
seob9960	4I	7.63e-04	seoa7443	4I	1.140826e-03
seoa8388	4I	7.64e-04	fcrc1855	4I	1.142061e-03
seob3303	4I	7.67e-04	ncr3713	4I	1.150048e-03
mioa4552	4I	7.78e-04	fcrc9269	4I	1.150659e-03
mioa4484	4I	7.8e-04	seob8368	4I	1.154981e-03
ncr8843	4I	7.83e-04	seob0122	4I	1.171391e-03
seoa9537	4I	7.83e-04	mioa0535	4I	1.173792e-03
seob9574	4I	7.88e-04	miob1062	4I	1.177608e-03
seob0308	4I	7.98e-04	seob1793	4I	1.177608e-03
mioa1193	4I	8.04e-04	seoc1593	4I	1.178329e-03
seob1318	4I	8.04e-04	miob9336	4I	1.178419e-03
hfcr6687	4I	8.17e-04	seob1862	4I	1.201035e-03
fcrc1496	4I	8.19e-04	seoa3105	4I	1.211669e-03
miob8320	4I	8.21e-04	seob3670	4I	1.23222e-03
seob0376	4I	8.21e-04	miob4867	4I	1.256093e-03
seoa8979	4I	8.23e-04	ncrc1140	4I	1.256093e-03
seoa9357	4I	8.24e-04	fcrc5720	4I	1.2614e-03
ncrb0782	4I	8.27e-04	miod6238	4I	1.278208e-03
seob3923	4I	8.31e-04	mioc7331	4I	1.301405e-03
ncr2293	4I	8.33e-04	ncrc6005	4I	1.305117e-03
seob0755	4I	8.35e-04	miod1942	4I	1.305311e-03
ncr0733	4I	8.46e-04	mioa0909	4I	1.312146e-03
hfcr5220	4I	8.48e-04	seob1879	4I	1.347303e-03
ncrc5844	4I	8.48e-04	miob6904	4I	1.355302e-03
mioa5355	4I	8.58e-04	mioc2880	4I	1.356947e-03
ncr8041	4I	8.61e-04	seob6368	4I	1.361315e-03
seob2994	4I	8.67e-04	ncr2472	4I	1.365497e-03
seob3119	4I	8.73e-04	ncrb8385	4I	1.369106e-03
fcrc8668	4I	8.75e-04	fcrc1756	4I	1.392986e-03
ncrc9784	4I	8.77e-04	miod6038	4I	1.395436e-03
seob6206	4I	8.88e-04	fcrc2088	4I	1.408465e-03
mioa6731	4I	8.9e-04	miob3348	4I	1.428182e-03
ncr5568	4I	9.0e-04	miod1195	4I	1.431152e-03
mioc4667	4I	9.01e-04	fcrc1879	4I	1.452287e-03
mioa5696	4I	9.03e-04	mioa6721	4I	1.457877e-03
hfcr1163	4I	9.1e-04	seoa3516	4I	1.46015e-03
ncr0808	4I	9.12e-04	ncr0025	4I	1.469905e-03
hfcr3019	4I	9.19e-04	hfcr1310	4I	1.478083e-03
fcrc3048	4I	9.26e-04	fcrc9959	4I	1.48762e-03
fcrc9454	4I	9.3e-04	fcrc5214	4I	1.490057e-03
seoa6315	4I	9.33e-04	ncrb4182	4I	1.50404e-03
fcrc9655	4I	9.37e-04	ncrb3702	4I	1.511682e-03
ncrc0715	4I	9.39e-04	mioa0577	4I	1.518616e-03
seoa8348	4I	9.56e-04	ncr8975	4I	1.524283e-03
fcrc9420	4I	9.64e-04	seob4579	4I	1.527065e-03

fcr4128	4I	1.53383e-03	mioc6987	4I	2.076534e-03
ncrc5162	4I	1.553082e-03	hfcr0624	4I	2.085152e-03
ncr5168	4I	1.55656e-03	ncrb3329	4I	2.085152e-03
ncrb3001	4I	1.557302e-03	seob6015	4I	2.09993e-03
miob3308	4I	1.566301e-03	fcr4782	4I	2.115262e-03
fcrb8187	4I	1.573331e-03	fcrb1733	4I	2.120875e-03
ncrb4039	4I	1.584396e-03	ncr0238	4I	2.1386e-03
miod1811	4I	1.590472e-03	mioc7895	4I	2.143605e-03
hfcr3500	4I	1.610297e-03	fcrb3718	4I	2.145161e-03
mioa8852	4I	1.618546e-03	seob6670	4I	2.155534e-03
mioa0494	4I	1.619093e-03	seob8501	4I	2.166556e-03
seoa0111	4I	1.622252e-03	miod2525	4I	2.174809e-03
ncr3782	4I	1.63287e-03	fcrb6187	4I	2.177878e-03
ncrc5569	4I	1.637974e-03	mioc6312	4I	2.199817e-03
mioc6075	4I	1.640004e-03	hfcr1733	4I	2.209362e-03
mioa4076	4I	1.665908e-03	ncrb4957	4I	2.210616e-03
seoa4305	4I	1.678116e-03	seob0089	4I	2.211811e-03
seob2185	4I	1.70771e-03	hfcr6651	4I	2.216864e-03
fcrc2090	4I	1.719751e-03	hfcr1302	4I	2.226095e-03
seoa9870	4I	1.728369e-03	seob4050	4I	2.226095e-03
seob1414	4I	1.747109e-03	fcrb2536	4I	2.230106e-03
seoa9828	4I	1.753504e-03	mioa8851	4I	2.23281e-03
fcrb3165	4I	1.760242e-03	seoa2012	4I	2.255872e-03
fcrc2099	4I	1.790284e-03	seoc1118	4I	2.258564e-03
seob1766	4I	1.794891e-03	fcr7419	4I	2.260166e-03
hfcr1743	4I	1.798381e-03	seob7432	4I	2.272415e-03
seob1908	4I	1.798381e-03	mioc4318	4I	2.279552e-03
seob4545	4I	1.798381e-03	fcrc0695	4I	2.279562e-03
fcrc5516	4I	1.799844e-03	fcr3121	4I	2.285067e-03
hfcr5228	4I	1.800664e-03	seoa8443	4I	2.285067e-03
mioa5692	4I	1.800664e-03	seoa1065	4I	2.312579e-03
seob4555	4I	1.800664e-03	miob4475	4I	2.330183e-03
fcrb1420	4I	1.801622e-03	ncrc9469	4I	2.33257e-03
fcr3595	4I	1.803204e-03	ncrc6592	4I	2.352328e-03
ncr2666	4I	1.803204e-03	seob4273	4I	2.355513e-03
fcrb8940	4I	1.834572e-03	hfcr6700	4I	2.362015e-03
miob5495	4I	1.838333e-03	seoa5577	4I	2.367648e-03
ncr3368	4I	1.838333e-03	seoa5235	4I	2.369839e-03
fcrb1807	4I	1.859263e-03	ncrb8273	4I	2.393454e-03
ncrc5054	4I	1.860924e-03	fcrb3134	4I	2.402582e-03
seob6525	4I	1.861275e-03	mioa9294	4I	2.412283e-03
seoc0924	4I	1.861444e-03	hfcr1697	4I	2.435634e-03
seoa8399	4I	1.88316e-03	ncrc5369	4I	2.435634e-03
fcrb8161	4I	1.885852e-03	seob5219	4I	2.439695e-03
mioa1520	4I	1.887743e-03	seoa5444	4I	2.479655e-03
fcrb8740	4I	1.892065e-03	seoa1173	4I	2.502414e-03
seob2810	4I	1.901388e-03	miob0189	4I	2.57178e-03
fcr5758	4I	1.909224e-03	miob2705	4I	2.574869e-03
mioc8423	4I	1.916815e-03	seoa8232	4I	2.578028e-03
hfcr5695	4I	1.956159e-03	fcr5123	4I	2.597097e-03
seoc4380	4I	1.956915e-03	mioa6854	4I	2.602922e-03
fcrb2871	4I	1.964974e-03	fcr0139	4I	2.651872e-03
ncrc0150	4I	1.985831e-03	fcr7004	4I	2.657357e-03
fcrb2060	4I	1.99746e-03	mioa9505	4I	2.658032e-03
hfcr0415	4I	1.99746e-03	seob7465	4I	2.711845e-03
seoa7555	4I	1.99746e-03	fcrb4409	4I	2.722505e-03
fcr2079	4I	2.016524e-03	seoc0276	4I	2.725532e-03
seob4560	4I	2.021887e-03	fcr0999	4I	2.730498e-03
seoc1025	4I	2.02575e-03	hfcr4488	4I	2.731117e-03
fcrb8080	4I	2.025786e-03	fcr3559	4I	2.734761e-03
seob0201	4I	2.050861e-03	mioa1660	4I	2.749542e-03
fcrb9720	4I	2.057033e-03	seoc0513	4I	2.753054e-03
fcr5470	4I	2.060807e-03	ncrc9712	4I	2.760324e-03
ncrc4079	4I	2.066895e-03	miod5707	4I	2.770552e-03

miob8711	4I	2.809832e-03	seoa6661	4I	3.644681e-03
seob3307	4I	2.811695e-03	seoa1720	4I	3.649977e-03
seoa9814	4I	2.836239e-03	seob2108	4I	3.666209e-03
seob9946	4I	2.84126e-03	ncr0478	4I	3.666381e-03
mioc7744	4I	2.845792e-03	fcrb2249	4I	3.695741e-03
seoa8543	4I	2.874349e-03	seob4117	4I	3.700072e-03
miob3898	4I	2.881671e-03	ncrb8134	4I	3.708615e-03
seoa8642	4I	2.881671e-03	seob9750	4I	3.708927e-03
mioa7140	4I	2.898369e-03	miob2492	4I	3.735778e-03
fcr4763	4I	2.928101e-03	mioa1971	4I	3.738256e-03
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fcrc1849	4I	2.952953e-03	miob8932	4I	3.752087e-03
fcrb1731	4I	2.954229e-03	ncrc4808	4I	3.775334e-03
fcrb3483	4I	2.983789e-03	mioa5085	4I	3.775842e-03
seoa4600	4I	2.998627e-03	seoa4586	4I	3.780119e-03
seoa0008	4I	3.007551e-03	seoa3408	4I	3.790116e-03
seob0168	4I	3.016761e-03	mioa8774	4I	3.812303e-03
seob2221	4I	3.044324e-03	seoa7546	4I	3.830009e-03
fcrb2933	4I	3.049655e-03	fcr3155	4I	3.832262e-03
ncrc5079	4I	3.050155e-03	ncr2182	4I	3.847974e-03
fcrb9481	4I	3.074875e-03	ncrc9557	4I	3.849741e-03
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seoa3533	4I	3.13784e-03	seoa6573	4I	3.875968e-03
miod5369	4I	3.159305e-03	fcrb2350	4I	3.883582e-03
seoa5683	4I	3.160612e-03	fcrb6009	4I	3.925377e-03
mioa0407	4I	3.167049e-03	miod7243	4I	3.934025e-03
fcrb7693	4I	3.203691e-03	ncrc3434	4I	3.939813e-03
seoa9160	4I	3.207335e-03	hfcr9613	4I	4.011004e-03
fcrb1552	4I	3.209013e-03	miob4055	4I	4.011569e-03
miob4836	4I	3.218792e-03	miob0154	4I	4.08718e-03
ncr0438	4I	3.245826e-03	seoa2442	4I	4.093483e-03
mioa0187	4I	3.279663e-03	seob3869	4I	4.093483e-03
mioa2374	4I	3.293401e-03	seoa2641	4I	4.10684e-03
ncrc0100	4I	3.298912e-03	seoa6620	4I	4.118774e-03
seob8741	4I	3.317878e-03	seoc3515	4I	4.159057e-03
ncrc2776	4I	3.322303e-03	fcrb9694	4I	4.20251e-03
ncrb3942	4I	3.332792e-03	ncrb7292	4I	4.220365e-03
ncrb0513	4I	3.349517e-03	miod4140	4I	4.240281e-03
ncr1387	4I	3.356296e-03	hfcr0045	4I	4.261381e-03
fcrb3017	4I	3.376066e-03	ncrc9877	4I	4.26595e-03
ncrc5091	4I	3.385978e-03	seoc2191	4I	4.272909e-03
miob8274	4I	3.404337e-03	mioc0567	4I	4.279318e-03
fcrc0241	4I	3.422538e-03	mioc3716	4I	4.281847e-03
seob0514	4I	3.423122e-03	fcrb3725	4I	4.312352e-03
ncr8866	4I	3.437719e-03	ncrc9772	4I	4.399985e-03
mioc7441	4I	3.437924e-03	miob8226	4I	4.470203e-03
fcrc6888	4I	3.449333e-03	mioa0380	4I	4.489956e-03
miob9065	4I	3.456747e-03	mioa1097	4I	4.509349e-03
mioa3514	4I	3.46245e-03	seob3462	4I	4.509349e-03
ncr3237	4I	3.46245e-03	mioa8811	4I	4.52055e-03
hfcr6406	4I	3.4643e-03	fcrc0959	4I	4.530274e-03
ncrc4991	4I	3.4643e-03	seob3154	4I	4.531125e-03
seob3499	4I	3.4643e-03	mioa0890	4I	4.570501e-03
ncrc9855	4I	3.46879e-03	fcrc6335	4I	4.58749e-03
miod6029	4I	3.517177e-03	ncrc5760	4I	4.601184e-03
ncr2013	4I	3.51941e-03	mioa1427	4I	4.633362e-03
seob4972	4I	3.531512e-03	ncrc3840	4I	4.633362e-03
hfcr0130	4I	3.533831e-03	seoa4040	4I	4.639931e-03
fcrb4378	4I	3.540302e-03	miod4348	4I	4.655192e-03
ncrc1643	4I	3.548484e-03	seoa7902	4I	4.66728e-03
mioc3726	4I	3.550472e-03	ncrc5150	4I	4.691321e-03
seob2188	4I	3.584274e-03	ncr1563	4I	4.707547e-03
seob2797	4I	3.6022e-03	seob4621	4I	4.707547e-03
seob1667	4I	3.640309e-03	fcrc7047	4I	4.744327e-03

seob5562	4I	4.746427e-03	mioa8647	4I	5.768458e-03
seoa4395	4I	4.779169e-03	mioa1445	4I	5.811166e-03
hfcr6468	4I	4.79651e-03	seoc3588	4I	5.826485e-03
ncrb8253	4I	4.799003e-03	ncrc3468	4I	5.832748e-03
seoa5986	4I	4.799003e-03	miob9052	4I	5.833135e-03
miob5736	4I	4.80808e-03	mioc5664	4I	5.835444e-03
seob3151	4I	4.834042e-03	fcrb2137	4I	5.84394e-03
seob9292	4I	4.848082e-03	hfcr5207	4I	5.84394e-03
seoa7517	4I	4.870405e-03	mioa2327	4I	5.859459e-03
fcrb4415	4I	4.898061e-03	fcrb9147	4I	5.861796e-03
mioa6621	4I	4.904983e-03	seob5458	4I	5.862878e-03
seob9649	4I	4.907044e-03	seoa5554	4I	5.877316e-03
mioc1122	4I	4.93196e-03	seoa1552	4I	5.896449e-03
ncrc6795	4I	4.933324e-03	seoa3230	4I	5.898784e-03
seoa3847	4I	4.942903e-03	fcr1844	4I	5.913324e-03
fcr5625	4I	4.99519e-03	fcrb5267	4I	5.942373e-03
ncr3684	4I	5.017654e-03	fcrb6896	4I	5.949973e-03
ncrb2091	4I	5.039376e-03	fcrc0094	4I	5.96467e-03
hfcr2287	4I	5.054567e-03	miob3684	4I	5.971717e-03
fcrc2576	4I	5.063792e-03	fcr6390	4I	6.000719e-03
seoa0501	4I	5.071997e-03	seob1737	4I	6.007946e-03
fcrc0430	4I	5.084925e-03	fcr2074	4I	6.018802e-03
hfcr0750	4I	5.09128e-03	fcr1883	4I	6.048593e-03
mioa3379	4I	5.102551e-03	fcr5536	4I	6.049129e-03
ncrc5672	4I	5.11611e-03	seoc2131	4I	6.08684e-03
fcr6497	4I	5.124127e-03	ncr4550	4I	6.099859e-03
mioa5468	4I	5.124127e-03	seoa0470	4I	6.100317e-03
seoa6923	4I	5.124127e-03	fcrb2218	4I	6.116835e-03
ncrc5500	4I	5.175143e-03	mioc7444	4I	6.13308e-03
mioa8946	4I	5.185969e-03	seoa3704	4I	6.146625e-03
fcr0056	4I	5.190905e-03	seob0321	4I	6.178138e-03
ncrc5039	4I	5.197151e-03	ncrb1337	4I	6.21911e-03
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fcrc4360	4I	5.250167e-03	ncrb6833	4I	6.229488e-03
fcrb4241	4I	5.25156e-03	ncr0075	4I	6.26855e-03
mioc0824	4I	5.254723e-03	mioa8952	4I	6.270044e-03
fcrc6563	4I	5.282794e-03	ncr0766	4I	6.276933e-03
seoa2122	4I	5.287317e-03	ncrc6817	4I	6.276933e-03
fcr0768	4I	5.301658e-03	mioa2013	4I	6.287512e-03
ncrc6479	4I	5.320657e-03	seob9485	4I	6.301111e-03
miod3254	4I	5.326719e-03	miod4142	4I	6.383134e-03
fcrc1745	4I	5.32716e-03	ncrc6712	4I	6.41394e-03
mioa4196	4I	5.344108e-03	fcr5779	4I	6.474618e-03
mioc8619	4I	5.353299e-03	seoa6197	4I	6.486591e-03
ncrc4654	4I	5.369673e-03	seob0703	4I	6.50097e-03
seob4515	4I	5.369673e-03	miob6821	4I	6.505915e-03
mioc2074	4I	5.414445e-03	ncrb8343	4I	6.552284e-03
ncr4545	4I	5.438486e-03	seoa5911	4I	6.597064e-03
seoa0029	4I	5.480759e-03	fcrb2292	4I	6.653984e-03
fcr0990	4I	5.490991e-03	seob4191	4I	6.654737e-03
fcrb1684	4I	5.495549e-03	fcrb2765	4I	6.689668e-03
seob0031	4I	5.509288e-03	miod5612	4I	6.698915e-03
seoa1856	4I	5.531453e-03	ncr4384	4I	6.700762e-03
fcrc6854	4I	5.540234e-03	seob4039	4I	6.713668e-03
fcrc2082	4I	5.550695e-03	fcrb5087	4I	6.714694e-03
seob2987	4I	5.569207e-03	fcrb5422	4I	6.7264e-03
mioa1473	4I	5.580693e-03	ncrc2119	4I	6.756046e-03
seob4030	4I	5.594557e-03	seob9552	4I	6.762169e-03
fcr3282	4I	5.608041e-03	fcrb3841	4I	6.780973e-03
fcr4795	4I	5.649808e-03	miob6988	4I	6.80749e-03
seob5726	4I	5.65605e-03	hfcr5473	4I	6.857537e-03
fcrb7852	4I	5.667225e-03	fcrc3415	4I	6.861942e-03
ncr1550	4I	5.713507e-03	fcr4380	4I	6.880921e-03
mioa0132	4I	5.738039e-03	ncr6335	4I	6.907692e-03

miod3079	4I	6.91873e-03	seoc2220	4I	8.240295e-03
seoa3628	4I	6.949533e-03	ncr0912	4I	8.275646e-03
seob9772	4I	6.956817e-03	seob0466	4I	8.285506e-03
mioa9581	4I	6.958796e-03	mioa9630	4I	8.304775e-03
ncr2486	4I	6.982956e-03	ncrb6192	4I	8.312148e-03
miob0877	4I	6.983468e-03	seoc2824	4I	8.3183e-03
seoa6137	4I	7.003723e-03	seoa0070	4I	8.335344e-03
fcr6415	4I	7.029261e-03	seoa1736	4I	8.342294e-03
seob1385	4I	7.029563e-03	seoa4070	4I	8.351138e-03
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ncrc1103	4I	7.109167e-03	miob2855	4I	8.459946e-03
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seoa2136	4I	7.196923e-03	seoa0913	4I	8.473584e-03
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mioa6093	4I	7.268139e-03	ncr2905	4I	8.640653e-03
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fcr6044	4I	7.452917e-03	seob5319	4I	8.811962e-03
seoa7078	4I	7.471779e-03	fcrc0654	4I	8.812335e-03
fcr6016	4I	7.53305e-03	miob1506	4I	8.830271e-03
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ncrb3585	4I	7.879438e-03	miod5672	4I	9.160361e-03
ncr0612	4I	7.925456e-03	seoa5933	4I	9.204501e-03
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seob9872	4I	7.94076e-03	ncrc0383	4I	9.294641e-03
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ncrb1373	4I	8.093663e-03	ncrc5553	4I	9.583937e-03
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seob4209	4I	8.135586e-03	seob0810	4I	9.583937e-03
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seoc4416	4I	9.841173e-03
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seob1737	4K	0.04	mioc4089	4M	7.46e-04
seoc5627	4K	0.04	mioc7362	4M	7.52e-04
fcr0860	4K	0.04	fcrc6976	4M	7.65e-04
seob3394	4K	0.04	seob9574	4M	7.88e-04
seob0046	4K	0.04	seoa8979	4M	8.23e-04
ncrc0704	4K	0.04	hfcr0478	4M	8.43e-04
miod6731	4K	0.04	ncr8041	4M	8.61e-04
ncr2591	4K	0.04	ncrc9784	4M	8.77e-04
seoa0740	4K	0.04	fcrc7102	4M	8.87e-04
mioc4696	4K	0.04	mioa6731	4M	8.9e-04
fcr7518	4K	0.04	fcrb2556	4M	8.98e-04
seob6198	4K	0.04	miob7156	4M	9.1e-04
mioa8314	4K	0.04	fcr2798	4M	9.78e-04
ncr2994	4K	0.04	hfcr6486	4M	9.83e-04
fcrb2015	4K	0.04	fcrb7240	4M	1.015969e-03
mioa5326	4K	0.04	hfcr5381	4M	1.016874e-03
hfcr1314	4K	0.04	miob7105	4M	1.073216e-03
miod7440	4M	2.44e-07	miob3982	4M	1.105438e-03
mioc7170	4M	2.53e-06	mioa3395	4M	1.154329e-03
mioc2561	4M	3.17e-06	ncrc0090	4M	1.185916e-03
fcrc3993	4M	4.37e-06	hfcr6406	4M	1.239885e-03
seoa6032	4M	5.48e-06	ncr4539	4M	1.309997e-03
miod5349	4M	6.31e-06	seoa1844	4M	1.345317e-03
seoa8894	4M	1.1e-05	mioc2348	4M	1.386736e-03
seob2697	4M	1.66e-05	miod6038	4M	1.395436e-03
ncr3751	4M	1.95e-05	ncr7753	4M	1.444958e-03
ncr7668	4M	4.63e-05	seob6486	4M	1.458125e-03
fcrb3578	4M	4.7e-05	fcr3101	4M	1.487316e-03
miod7421	4M	6.08e-05	ncrb3001	4M	1.557302e-03
mioa1370	4M	8.87e-05	miod1811	4M	1.590472e-03
mioc8410	4M	9.18e-05	seoa9740	4M	1.598061e-03
seoa9482	4M	9.27e-05	mioa3080	4M	1.603678e-03
fcrb7339	4M	9.87e-05	mioa0494	4M	1.619093e-03
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fcrb0265	4M	1.2e-04	ncrc1367	4M	1.650171e-03
seob6189	4M	1.32e-04	mioa1015	4M	1.68644e-03
miod7414	4M	1.36e-04	seob0304	4M	1.693307e-03
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fcr0253	4M	1.45e-04	fcrb3165	4M	1.760242e-03
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seob6851	4M	1.55e-04	fcrc5516	4M	1.799844e-03
fcrb3461	4M	1.6e-04	fcrb8940	4M	1.834572e-03
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fcr4582	4M	2.27e-04	ncrc9729	4M	1.919544e-03
fcrc1381	4M	2.28e-04	seoc4380	4M	1.956915e-03
seob0065	4M	2.35e-04	miod0592	4M	1.985622e-03
seoc0999	4M	2.44e-04	ncr5397	4M	2.00365e-03
mioc2726	4M	2.7e-04	seob4560	4M	2.021887e-03
mioc6260	4M	2.92e-04	mioc0824	4M	2.034483e-03
fcrc0112	4M	3.06e-04	mioc1107	4M	2.070013e-03
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ncrb8714	4M	3.16e-04	fcrc6916	4M	2.121527e-03
seoa2949	4M	3.29e-04	miod2525	4M	2.174809e-03
fcr5779	4M	4.02e-04	fcrb2624	4M	2.174826e-03
miob7922	4M	4.07e-04	fcr3121	4M	2.234303e-03
fcrb7830	4M	4.09e-04	fcrc0695	4M	2.279562e-03
mioc2911	4M	4.49e-04	miob1326	4M	2.329343e-03
fcrl463	4M	4.77e-04	miod6467	4M	2.34447e-03

mioa1976	4M	2.452224e-03	ncrb1398	4M	5.295501e-03
fcrc5142	4M	2.464685e-03	miod3854	4M	5.307923e-03
seoa3670	4M	2.543649e-03	miod3254	4M	5.326719e-03
ncrc1578	4M	2.579378e-03	mioc8619	4M	5.353299e-03
miod4332	4M	2.601957e-03	ncrc9758	4M	5.427537e-03
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fcrb4409	4M	2.722505e-03	fcrc6560	4M	5.571911e-03
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mioc3962	4M	2.824707e-03	fcrb5164	4M	5.814619e-03
seob4545	4M	2.842281e-03	seoa4524	4M	5.958281e-03
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mioa0702	4M	2.977964e-03	seob3520	4M	6.215767e-03
seob9649	4M	2.997767e-03	ncrb1337	4M	6.21911e-03
seoa6304	4M	3.095502e-03	ncrb1515	4M	6.341156e-03
mioa2185	4M	3.147097e-03	ncrc6000	4M	6.444479e-03
mioa3856	4M	3.151528e-03	hfcr4176	4M	6.494359e-03
mioa0187	4M	3.279663e-03	fcrb8187	4M	6.498087e-03
mioa2374	4M	3.293401e-03	seob0703	4M	6.50097e-03
fcrb3017	4M	3.376066e-03	fcr4469	4M	6.567393e-03
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miob9065	4M	3.456747e-03	ncr4545	4M	6.618737e-03
seob4972	4M	3.531512e-03	mioa1303	4M	6.633139e-03
seob2797	4M	3.6022e-03	ncr7631	4M	6.713476e-03
seoa1749	4M	3.637644e-03	fcrb8536	4M	6.791086e-03
ncr0451	4M	3.707725e-03	hfcr5987	4M	6.867295e-03
fcr6018	4M	3.762242e-03	ncr9956	4M	6.920421e-03
seoa1480	4M	3.790975e-03	ncr0240	4M	6.999641e-03
hfcr0370	4M	3.8121e-03	mioa1337	4M	7.012816e-03
seob1187	4M	3.817075e-03	ncrb8207	4M	7.041692e-03
fcr3155	4M	3.832262e-03	hfcr1914	4M	7.057729e-03
ncr2182	4M	3.847974e-03	mioa1427	4M	7.073426e-03
seoa6573	4M	3.875968e-03	mioa6093	4M	7.268139e-03
seob0200	4M	3.979023e-03	seob6560	4M	7.500236e-03
ncrc5492	4M	4.081573e-03	mioc6925	4M	7.512586e-03
mioc0741	4M	4.154883e-03	ncrc3936	4M	7.54805e-03
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mioc0567	4M	4.279318e-03	fcrb9655	4M	7.792172e-03
mioc3716	4M	4.281847e-03	seob6177	4M	7.843092e-03
fcrb8467	4M	4.415815e-03	miob7309	4M	8.045055e-03
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ncrc5150	4M	4.691321e-03	seoc2220	4M	8.240295e-03
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fcr0707	4M	4.772856e-03	hfcr5737	4M	8.332211e-03
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seoa1213	4M	0.02
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mioc2451	4M	0.03
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fcrc6970	4M	0.03
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mioa2818	4M	0.03

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seoc5627	4M	0.04
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miob7554	40	0.01	fcrb3550	40	0.01
ncrc7085	40	0.01	fcr4272	40	0.01
seob5636	40	0.01	ncrc9159	40	0.01
seob7907	40	0.01	fcrb2426	40	0.01
ncrc5813	40	0.01	seob2077	40	0.01
ncr7267	40	0.01	miod6134	40	0.01
seoc0705	40	0.01	fcrb1729	40	0.01
fcrb4542	40	0.01	ncrc2859	40	0.01
mioa1079	40	0.01	miob0189	40	0.01
hfcr3413	40	0.01	ncrc4033	40	0.01
miob0973	40	0.01	mioa0152	40	0.01
hfcr1709	40	0.01	ncrb7102	40	0.01
fcr5222	40	0.01	ncr0808	40	0.01
seoc3870	40	0.01	seob9334	40	0.01
fcrb2353	40	0.01	hfcr1641	40	0.01

seoa1353	40	0.01
seoa5578	40	0.01
fcrb9856	40	0.01
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mioc4983	40	0.01
fcrb4696	40	0.01
seob5773	40	0.01
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fcrb4294	40	0.01
mioa1520	40	0.01
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mioc6949	40	0.01
miod2707	40	0.01
ncrc2273	40	0.01
ncrc5608	40	0.01
ncrb0262	40	0.01
seob7744	40	0.01
ncrc3072	40	0.01
ncrc1952	40	0.01
ncrc7092	40	0.02
ncrb7166	40	0.02
fcrb1381	40	0.02
seob1617	40	0.02
miob8487	40	0.02
mioc4766	40	0.02
seob3533	40	0.02
miob4712	40	0.02
seoc3965	40	0.02
ncrc4885	40	0.02
hfcr3834	40	0.02
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mioa8548	40	0.02
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mioc8057	40	0.02
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mioa0647	40	0.02
seob6041	40	0.02
seob4192	40	0.02
miod1389	40	0.02
fcrb6937	40	0.02
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fcrb9859	40	0.02
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ncr5713	40	0.02
seob3370	40	0.02
ncr5939	40	0.02
seoc1948	40	0.02
fcrc4421	40	0.02
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seob1008	40	0.02
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ncrb7726	40	0.02
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fcrb2876	40	0.02

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fcrc4896	40	0.02
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fcrc4408	40	0.02
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hfcr2598	40	0.02
seoc1934	40	0.02
fcrc0332	40	0.02
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mioc2997	40	0.02
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seob8807	40	0.02
seob4030	40	0.02
miob0178	40	0.02
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seob0872	40	0.02
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seob2163	40	0.02	fcrc2131	40	0.02
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fcrb3086	40	0.02	seoa8640	40	0.02
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seob1118	40	0.02	ncrc3551	40	0.02
fcrb6099	40	0.02	miob3690	40	0.02
fcrb1312	40	0.02	seob4689	40	0.02
fcrb6734	40	0.02	seoa3556	40	0.02
seoa6658	40	0.02	fcr4128	40	0.02
ncrc0640	40	0.02	seoa0023	40	0.02
fcr5425	40	0.02	ncrc1595	40	0.02
fcr1772	40	0.02	mioc7260	40	0.02
mioa8773	40	0.02	fcrc2431	40	0.02
fcr5889	40	0.02	miod6835	40	0.02
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miob3456	40	0.02	seob5080	40	0.03
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fcrb8226	40	0.02	fcrc6413	40	0.03
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seoa4023	40	0.02	seob2134	40	0.03
ncrb2798	40	0.02	seob2750	40	0.03
seoa4158	40	0.02	fcr2798	40	0.03
fcrb1720	40	0.02	ncr3465	40	0.03
fcrc7228	40	0.02	miod5962	40	0.03
mioa0684	40	0.02	fcrb3874	40	0.03
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mioc3208	40	0.02	mioa0862	40	0.03
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fcrb2546	40	0.02	seob0182	40	0.03
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fcrb1724	40	0.04	seoc2029	4Q	6.23e-07
mioc2887	40	0.04	mioc7170	4Q	2.53e-06
seob1748	40	0.04	mioc2561	4Q	3.17e-06
fcrb3283	40	0.04	mioa2072	4Q	3.26e-06
fcrb7944	40	0.04	seob4419	4Q	4.27e-06
fcr6708	40	0.04	fcrc3993	4Q	4.37e-06
mioa8946	40	0.04	seoa6032	4Q	5.48e-06
seoc5285	40	0.04	miod5349	4Q	6.31e-06
mioa1584	40	0.04	seoa8894	4Q	1.1e-05
fcr4832	40	0.04	ncr3751	4Q	1.95e-05
fcrb3015	40	0.04	seoa4518	4Q	2.47e-05
miob3618	40	0.04	seoa8566	4Q	3.22e-05
miob8191	40	0.04	fcrb3578	4Q	4.7e-05
mioc1357	40	0.04	seoa9373	4Q	6.54e-05
hfcrc2890	40	0.04	mioa1370	4Q	8.87e-05
seob4197	40	0.04	seoa9482	4Q	9.27e-05
ncr2304	40	0.04	fcr4477	4Q	1.01e-04
mioc2133	40	0.04	fcrb0265	4Q	1.2e-04
ncr7151	40	0.04	mioc2094	4Q	1.38e-04
ncrc9491	40	0.04	ncr3262	4Q	1.4e-04
fcr2861	40	0.04	ncr0223	4Q	1.5e-04
seob0818	40	0.04	fcrb2536	4Q	1.53e-04
fcrb2199	40	0.04	seob6851	4Q	1.55e-04
seoc3277	40	0.04	fcrb5850	4Q	1.56e-04
seoc1058	40	0.04	miob8812	4Q	1.56e-04
seob1848	40	0.04	miod5651	4Q	1.77e-04
miod5126	40	0.04	hfcrc2390	4Q	1.83e-04
ncrb3585	40	0.04	fcr4582	4Q	2.27e-04
fcrb2301	40	0.04	miob0167	4Q	2.32e-04
mioa9604	40	0.04	fcrc5937	4Q	2.36e-04
seoc0698	40	0.04	seoc0999	4Q	2.44e-04
fcrb8668	40	0.04	fcrc0554	4Q	2.48e-04
fcrc4663	40	0.04	hfcrc1073	4Q	2.54e-04
mioa1906	40	0.04	seob4191	4Q	2.69e-04
seoa1802	40	0.04	mioc2726	4Q	2.7e-04
fcr5930	40	0.04	miob8694	4Q	2.87e-04
seoa4264	40	0.04	seoa4053	4Q	3.03e-04
seob4999	40	0.04	fcrc0112	4Q	3.06e-04
miod6058	40	0.04	ncr1631	4Q	3.07e-04



ncrb8714	4Q	3.16e-04	ncrc0150	4Q	1.985831e-03
fcr2573	4Q	3.43e-04	miod5894	4Q	2.014527e-03
seob7584	4Q	3.63e-04	miod0340	4Q	2.021229e-03
fcr5779	4Q	4.02e-04	seob4560	4Q	2.021887e-03
ncrc5663	4Q	5.0e-04	mioc0824	4Q	2.034483e-03
ncrc4757	4Q	5.23e-04	miob9163	4Q	2.097664e-03
seoa7530	4Q	5.56e-04	fcrb9843	4Q	2.120966e-03
seoc6703	4Q	5.75e-04	miod2525	4Q	2.174809e-03
seob9145	4Q	6.11e-04	fcrb2624	4Q	2.174826e-03
mioa2537	4Q	6.62e-04	fcrb6187	4Q	2.177878e-03
mioa6418	4Q	7.09e-04	seoa0115	4Q	2.17824e-03
mioc7362	4Q	7.52e-04	seoc1906	4Q	2.1992e-03
seob9960	4Q	7.63e-04	fcr3121	4Q	2.234303e-03
seoa8388	4Q	7.64e-04	fcrc0695	4Q	2.279562e-03
fcrc6976	4Q	7.65e-04	fcrc6016	4Q	2.3165e-03
seob3303	4Q	7.67e-04	miob1326	4Q	2.329343e-03
seob9574	4Q	7.88e-04	miob4475	4Q	2.330183e-03
seoa8979	4Q	8.23e-04	miod6467	4Q	2.34447e-03
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ncrc2080	4Q	8.53e-04	fcrc5142	4Q	2.464685e-03
mioa5355	4Q	8.58e-04	miob8143	4Q	2.489145e-03
ncr8041	4Q	8.61e-04	seoa3670	4Q	2.543649e-03
fcr0824	4Q	8.62e-04	ncrc1578	4Q	2.579378e-03
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mioa6731	4Q	8.9e-04	seoc1402	4Q	2.660096e-03
fcrb2556	4Q	8.98e-04	seoc0276	4Q	2.725532e-03
mioc4667	4Q	9.01e-04	seob3307	4Q	2.811695e-03
miob7156	4Q	9.1e-04	seoa9814	4Q	2.836239e-03
fcrc3048	4Q	9.26e-04	seob4545	4Q	2.842281e-03
fcr2798	4Q	9.78e-04	fcrb4391	4Q	2.852331e-03
seoc1996	4Q	9.81e-04	fcr0224	4Q	2.870823e-03
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miod5310	4Q	1.129688e-03	ncrc3464	4Q	2.965232e-03
mioa3395	4Q	1.154329e-03	mioa0702	4Q	2.977964e-03
fcrb1539	4Q	1.177578e-03	seob9649	4Q	2.997767e-03
miob9336	4Q	1.178419e-03	seob2221	4Q	3.044324e-03
ncrc0090	4Q	1.185916e-03	mioa2185	4Q	3.147097e-03
hfcr6406	4Q	1.239885e-03	mioa3856	4Q	3.151528e-03
miod1942	4Q	1.305311e-03	seoa5683	4Q	3.160612e-03
ncr4539	4Q	1.309997e-03	mioa0187	4Q	3.279663e-03
seoa1844	4Q	1.345317e-03	mioa2374	4Q	3.293401e-03
mioc2880	4Q	1.356947e-03	fcr5075	4Q	3.353508e-03
mioc2348	4Q	1.386736e-03	ncrb0145	4Q	3.359507e-03
mioc6987	4Q	1.45158e-03	miob8274	4Q	3.404337e-03
fcr3101	4Q	1.487316e-03	miob9065	4Q	3.456747e-03
ncr7595	4Q	1.511845e-03	fcrb2307	4Q	3.463155e-03
fcr4128	4Q	1.53383e-03	miob7290	4Q	3.492188e-03
ncrb3001	4Q	1.557302e-03	seob2797	4Q	3.6022e-03
fcrb8187	4Q	1.573331e-03	seoa1749	4Q	3.637644e-03
miod1811	4Q	1.590472e-03	ncr0451	4Q	3.707725e-03
mioa3080	4Q	1.603678e-03	fcr6018	4Q	3.762242e-03
mioc0052	4Q	1.624699e-03	seoa1480	4Q	3.790975e-03
miob9209	4Q	1.634228e-03	hfcr0370	4Q	3.8121e-03
ncrc1367	4Q	1.650171e-03	seoa6573	4Q	3.875968e-03
ncr5719	4Q	1.677652e-03	mioc7084	4Q	3.93591e-03
mioa1015	4Q	1.68644e-03	seob0200	4Q	3.979023e-03
seob6853	4Q	1.718429e-03	ncrc5492	4Q	4.081573e-03
fcrc2099	4Q	1.790284e-03	miod6018	4Q	4.139368e-03
seob1766	4Q	1.794891e-03	mioc0741	4Q	4.154883e-03
seob6506	4Q	1.826439e-03	ncrc4531	4Q	4.208322e-03
ncrc9729	4Q	1.919544e-03	miod4140	4Q	4.240281e-03
miod0592	4Q	1.985622e-03	fcrb9649	4Q	4.270145e-03

mioc0567	4Q	4.279318e-03	mioa0249	4Q	7.184179e-03
fcrc0959	4Q	4.530274e-03	seoa9935	4Q	7.197022e-03
fcrb2318	4Q	4.630688e-03	ncrc6687	4Q	7.304834e-03
miod4686	4Q	4.657868e-03	seob1191	4Q	7.325599e-03
seoa7129	4Q	4.719984e-03	miob4058	4Q	7.329008e-03
ncrb4912	4Q	4.752707e-03	fcrb8542	4Q	7.350932e-03
ncr3369	4Q	4.770221e-03	fcf5723	4Q	7.369143e-03
fcf0707	4Q	4.772856e-03	seoc3993	4Q	7.378389e-03
mioa6739	4Q	4.778158e-03	seob6560	4Q	7.500236e-03
fcfb5438	4Q	4.92339e-03	mioc6925	4Q	7.512586e-03
mioa9831	4Q	4.946737e-03	ncrc3936	4Q	7.54805e-03
fcfb3192	4Q	4.985296e-03	miob4221	4Q	7.572537e-03
ncr3684	4Q	5.017654e-03	seob2169	4Q	7.634987e-03
seob1318	4Q	5.055898e-03	ncrc6087	4Q	7.662274e-03
fcfb8942	4Q	5.08231e-03	hfcr0517	4Q	7.704251e-03
fcrc0430	4Q	5.084925e-03	fcfb9655	4Q	7.792172e-03
miob8583	4Q	5.097523e-03	ncrc4226	4Q	7.824984e-03
ncrc5672	4Q	5.11611e-03	seob6177	4Q	7.843092e-03
miob6364	4Q	5.172374e-03	mioc7998	4Q	7.939586e-03
ncrc5500	4Q	5.175143e-03	miob7309	4Q	8.045055e-03
seob3204	4Q	5.176722e-03	fcrc0295	4Q	8.130412e-03
ncr3313	4Q	5.18529e-03	miod2665	4Q	8.152135e-03
miod2639	4Q	5.218734e-03	miob1493	4Q	8.197903e-03
miod3592	4Q	5.253602e-03	fcf0593	4Q	8.19812e-03
fcrc6563	4Q	5.282794e-03	ncrb3077	4Q	8.265993e-03
miod3854	4Q	5.307923e-03	hfcr5737	4Q	8.332211e-03
miod3254	4Q	5.326719e-03	seoa4070	4Q	8.351138e-03
fcrc1745	4Q	5.32716e-03	fcfb1684	4Q	8.355442e-03
ncrc9758	4Q	5.427537e-03	ncrc6264	4Q	8.530558e-03
fcf0990	4Q	5.490991e-03	ncrc1502	4Q	8.575665e-03
fcfb6650	4Q	5.525357e-03	fcf0770	4Q	8.634112e-03
fcrc2082	4Q	5.550695e-03	miob1506	4Q	8.830271e-03
fcfb7852	4Q	5.667225e-03	miod1331	4Q	8.912821e-03
fcf0253	4Q	5.72015e-03	mioa2413	4Q	9.000025e-03
fcfb5164	4Q	5.814619e-03	fcfb3894	4Q	9.03812e-03
fcfb1687	4Q	5.960627e-03	fcfb2299	4Q	9.0502e-03
fcf1883	4Q	6.048593e-03	miob3461	4Q	9.117224e-03
fcf5536	4Q	6.049129e-03	miod1574	4Q	9.196145e-03
ncrc0663	4Q	6.085718e-03	fcfb7339	4Q	9.198522e-03
fcf0608	4Q	6.096137e-03	seoa2391	4Q	9.263207e-03
ncrc0342	4Q	6.197336e-03	ncrc0101	4Q	9.315893e-03
ncrb1337	4Q	6.21911e-03	seoa1737	4Q	9.470911e-03
ncrb1515	4Q	6.341156e-03	mioc4835	4Q	9.495048e-03
ncrc0139	4Q	6.437649e-03	fcfb6220	4Q	9.620246e-03
ncrc6000	4Q	6.444479e-03	fcrc5846	4Q	9.622113e-03
hfcr4176	4Q	6.494359e-03	fcf3367	4Q	9.80502e-03
seob0703	4Q	6.50097e-03	fcfb3466	4Q	9.829055e-03
fcf4469	4Q	6.567393e-03	ncrc7038	4Q	9.905278e-03
mioc2166	4Q	6.609859e-03	mioc4022	4Q	9.984425e-03
mioa1303	4Q	6.633139e-03	miob8214	4Q	0.01
fcfb9352	4Q	6.647947e-03	mioc4366	4Q	0.01
seob5500	4Q	6.672454e-03	miod4142	4Q	0.01
fcfb8536	4Q	6.791086e-03	fcfb2713	4Q	0.01
fcrc1607	4Q	6.799098e-03	fcfb1787	4Q	0.01
hfcr1760	4Q	6.835569e-03	mioa2580	4Q	0.01
hfcr5987	4Q	6.867295e-03	fcfb4988	4Q	0.01
ncr6335	4Q	6.907692e-03	seob3520	4Q	0.01
seoa4366	4Q	6.910667e-03	fcf0903	4Q	0.01
miod3079	4Q	6.91873e-03	miob4037	4Q	0.01
ncrc2495	4Q	6.966429e-03	mioa5692	4Q	0.01
ncrb8207	4Q	7.041692e-03	seob4036	4Q	0.01
ncrc6813	4Q	7.043646e-03	fcf1068	4Q	0.01
mioa1427	4Q	7.073426e-03	mioa2993	4Q	0.01
seob7474	4Q	7.109226e-03	miob2743	4Q	0.01

mioc3618	4Q	0.01
fcrb5918	4Q	0.01
mioa5461	4Q	0.01
ncrb8451	4Q	0.01
fcrb5100	4Q	0.01
fcrb2818	4Q	0.01
miod7457	4Q	0.01
seob3887	4Q	0.01
fcr2598	4Q	0.01
seoa0003	4Q	0.01
fcrb3135	4Q	0.01
hfcr5970	4Q	0.01
miod4464	4Q	0.01
fcrb3702	4Q	0.01
fcrb8432	4Q	0.01
hfcr5237	4Q	0.01
ncrc0304	4Q	0.01
ncrc5930	4Q	0.01
fcrb5422	4Q	0.01
fcrb7588	4Q	0.01
seob8693	4Q	0.01
fcrb1202	4Q	0.01
ncrc5959	4Q	0.01
seob6368	4Q	0.01
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mioa5691	4Q	0.01
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miod6961	4Q	0.01
fcrb7808	4Q	0.01
mioa2213	4Q	0.01
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mioa4014	4Q	0.01
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fcr7705	4Q	0.01
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seoa8854	4Q	0.02
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seoa8640	4Q	0.02
miob4876	4Q	0.02
fcrc6228	4Q	0.02
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seoa0470	4Q	0.03
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mioa0497	4Q	0.03
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fcr2196	4Q	0.03
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ncrc1615	4Q	0.03	miod5349	4S	6.31e-06
fcrb3083	4Q	0.03	seoa8894	4S	1.1e-05
mioa2343	4Q	0.03	fcrb4534	4S	1.46e-05
ncrc4000	4Q	0.04	seob2697	4S	1.66e-05
ncr3934	4Q	0.04	seoa4518	4S	2.47e-05
miob9284	4Q	0.04	miob6562	4S	2.52e-05
fcr4984	4Q	0.04	seoa8566	4S	3.22e-05
ncr4538	4Q	0.04	miod5123	4S	5.49e-05
ncrb1833	4Q	0.04	seob4333	4S	5.73e-05
fcrb5177	4Q	0.04	miod7421	4S	6.08e-05
seob5465	4Q	0.04	mioa1370	4S	8.87e-05
fcrb8467	4Q	0.04	fcrb7339	4S	9.87e-05
hfcr5522	4Q	0.04	fcr4477	4S	1.01e-04
miob5752	4Q	0.04	fcrb0265	4S	1.2e-04
mioc4131	4Q	0.04	seob6189	4S	1.32e-04
ncrc6459	4Q	0.04	mioc2094	4S	1.38e-04
fcrb6818	4Q	0.04	fcr0253	4S	1.45e-04
seoa3121	4Q	0.04	seoa7652	4S	1.5e-04
miob6595	4Q	0.04	fcrb2536	4S	1.53e-04
miod0455	4Q	0.04	fcrb5850	4S	1.56e-04
seob0266	4Q	0.04	miob8812	4S	1.56e-04
seoa0860	4Q	0.04	fcrb3461	4S	1.6e-04
ncr0531	4Q	0.04	seob4029	4S	1.69e-04
fcrc1019	4Q	0.04	miod5651	4S	1.77e-04
ncrc4875	4Q	0.04	seob5748	4S	1.79e-04
ncrc5738	4Q	0.04	hfcr2390	4S	1.83e-04
ncrc0217	4Q	0.04	miod5505	4S	1.89e-04
fcrb3283	4Q	0.04	seoc2264	4S	2.1e-04
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mioc4086	4Q	0.04	fcrc1381	4S	2.28e-04
seob6582	4Q	0.04	miob0167	4S	2.32e-04
ncrc9039	4Q	0.04	seoc1175	4S	2.33e-04
ncr0132	4Q	0.04	fcrc5937	4S	2.36e-04
fcr6181	4Q	0.04	fcrc0554	4S	2.48e-04
miob2668	4Q	0.04	seob4191	4S	2.69e-04
seob3394	4Q	0.04	miob8694	4S	2.87e-04
miod5126	4Q	0.04	ncr0153	4S	3.07e-04
miod6731	4Q	0.04	seoa4366	4S	3.08e-04
seoa0792	4Q	0.04	seoc6169	4S	3.11e-04
miob9248	4Q	0.04	ncrb8714	4S	3.16e-04
ncr2591	4Q	0.04	fcr2573	4S	3.43e-04
fcrb5639	4Q	0.04	fcrb3578	4S	3.7e-04
fcr5930	4Q	0.04	fcr5779	4S	4.02e-04
seoa4606	4Q	0.04	ncrc5663	4S	5.0e-04
mioc4696	4Q	0.04	mioc2602	4S	5.18e-04
fcr7518	4Q	0.04	seoc6703	4S	5.75e-04
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miod2412	4Q	0.04	seob9145	4S	6.11e-04
seob1972	4Q	0.04	mioa6418	4S	7.09e-04
miob7913	4Q	0.04	miod1925	4S	7.23e-04
fcr3053	4Q	0.04	mioc4089	4S	7.46e-04
seob6198	4Q	0.04	mioc7362	4S	7.52e-04
fcrb2015	4Q	0.04	seob9960	4S	7.63e-04
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hfcr1314	4Q	0.04	seob3303	4S	7.67e-04
seoc2029	4S	6.23e-07	ncrc2080	4S	8.53e-04
mioc7170	4S	2.53e-06	mioa5355	4S	8.58e-04
mioa2072	4S	3.26e-06	ncr8041	4S	8.61e-04
seob5523	4S	4.23e-06	ncrc9784	4S	8.77e-04
seob4419	4S	4.27e-06	fcrc7102	4S	8.87e-04
fcrc3993	4S	4.37e-06	mioa6731	4S	8.9e-04
seoa4461	4S	5.29e-06	mioc4667	4S	9.01e-04

fcrc3048	4S	9.26e-04	seob4972	4S	3.531512e-03
fcrb9420	4S	9.64e-04	mioc3726	4S	3.550472e-03
seoc1996	4S	9.81e-04	seob2797	4S	3.6022e-03
hfcr5381	4S	1.016874e-03	fcr6018	4S	3.762242e-03
fcrb1539	4S	1.177578e-03	fcr3155	4S	3.832262e-03
miob9336	4S	1.178419e-03	ncr2182	4S	3.847974e-03
miod1942	4S	1.305311e-03	mioc7084	4S	3.93591e-03
mioa0909	4S	1.312146e-03	miod6018	4S	4.139368e-03
mioc2880	4S	1.356947e-03	miod4140	4S	4.240281e-03
mioc2348	4S	1.386736e-03	fcrb9649	4S	4.270145e-03
miod6038	4S	1.395436e-03	seoa9711	4S	4.329889e-03
fcr3101	4S	1.487316e-03	miob8226	4S	4.470203e-03
fcr4128	4S	1.53383e-03	mioa0890	4S	4.570501e-03
ncrc5162	4S	1.553082e-03	fcrb2318	4S	4.630688e-03
ncrb3001	4S	1.557302e-03	miod4686	4S	4.657868e-03
miod1811	4S	1.590472e-03	seoa7129	4S	4.719984e-03
seoa9740	4S	1.598061e-03	mioa6739	4S	4.778158e-03
mioa0494	4S	1.619093e-03	mioa0826	4S	4.884238e-03
mioc0052	4S	1.624699e-03	mioa6621	4S	4.904983e-03
miob9209	4S	1.634228e-03	fcrb5438	4S	4.92339e-03
ncrc1367	4S	1.650171e-03	mioa9831	4S	4.946737e-03
seoa4305	4S	1.678116e-03	fcrc6174	4S	4.953862e-03
seob0304	4S	1.693307e-03	fcrb3192	4S	4.985296e-03
fcrb3165	4S	1.760242e-03	ncr3684	4S	5.017654e-03
fcrc2099	4S	1.790284e-03	seob1318	4S	5.055898e-03
seob1766	4S	1.794891e-03	fcrc0430	4S	5.084925e-03
fcrc5516	4S	1.799844e-03	ncrc5672	4S	5.11611e-03
seob6506	4S	1.826439e-03	ncr2862	4S	5.163569e-03
ncrc5054	4S	1.860924e-03	miob6364	4S	5.172374e-03
seoc4380	4S	1.956915e-03	ncrc5500	4S	5.175143e-03
miod0592	4S	1.985622e-03	seob3204	4S	5.176722e-03
ncrc0150	4S	1.985831e-03	miod3592	4S	5.253602e-03
miod5894	4S	2.014527e-03	mioc0824	4S	5.254723e-03
miod0340	4S	2.021229e-03	ncrb1398	4S	5.295501e-03
seob4560	4S	2.021887e-03	miod3254	4S	5.326719e-03
miob9163	4S	2.097664e-03	mioc8619	4S	5.353299e-03
fcrb9843	4S	2.120966e-03	fcr0990	4S	5.490991e-03
ncr0238	4S	2.1386e-03	fcrb1684	4S	5.495549e-03
miod2525	4S	2.174809e-03	fcrb6650	4S	5.525357e-03
fcrb2624	4S	2.174826e-03	fcr3282	4S	5.608041e-03
seoa0115	4S	2.17824e-03	fcrb7852	4S	5.667225e-03
fcr3121	4S	2.234303e-03	ncrc4654	4S	5.866006e-03
fcr7419	4S	2.260166e-03	fcrb1687	4S	5.960627e-03
fcrc0695	4S	2.279562e-03	fcr6390	4S	6.000719e-03
seoa1065	4S	2.312579e-03	fcr1883	4S	6.048593e-03
fcrc6016	4S	2.3165e-03	fcr5536	4S	6.049129e-03
miob4475	4S	2.330183e-03	hfcr3500	4S	6.054096e-03
ncrc1578	4S	2.579378e-03	seoa0470	4S	6.100317e-03
mioc8434	4S	2.661058e-03	ncrc6712	4S	6.41394e-03
seoc0276	4S	2.725532e-03	ncrc0139	4S	6.437649e-03
fcr0999	4S	2.730498e-03	fcrb8187	4S	6.498087e-03
fcrb4391	4S	2.852331e-03	mioa1303	4S	6.633139e-03
fcr0224	4S	2.870823e-03	fcrb2765	4S	6.689668e-03
mioa7140	4S	2.898369e-03	miod5612	4S	6.698915e-03
ncrc6359	4S	2.898846e-03	fcrb5087	4S	6.714694e-03
seob2221	4S	3.044324e-03	fcrc1607	4S	6.799098e-03
fcrb2933	4S	3.049655e-03	hfcr1760	4S	6.835569e-03
mioa2185	4S	3.147097e-03	miod3079	4S	6.91873e-03
seoa5683	4S	3.160612e-03	ncrc2495	4S	6.966429e-03
mioa2374	4S	3.293401e-03	hfcr1914	4S	7.057729e-03
ncrb0145	4S	3.359507e-03	mioa1427	4S	7.073426e-03
fcrb3017	4S	3.376066e-03	mioa0249	4S	7.184179e-03
miob8274	4S	3.404337e-03	seoa9935	4S	7.197022e-03
fcrb2307	4S	3.463155e-03	mioa6093	4S	7.268139e-03

miob4058	4S	7.329008e-03	fcrb3897	4S	0.01
fcrb8542	4S	7.350932e-03	fcrc4948	4S	0.01
seoc3993	4S	7.378389e-03	mioc7471	4S	0.01
seoa7078	4S	7.471779e-03	seob0344	4S	0.01
miob4221	4S	7.572537e-03	miob1829	4S	0.01
hfcr0517	4S	7.704251e-03	mioc3092	4S	0.01
ncrc4226	4S	7.824984e-03	ncrb5737	4S	0.01
mioc7998	4S	7.939586e-03	fcrb5675	4S	0.01
fcrb1329	4S	8.164602e-03	mioc8016	4S	0.01
miob1493	4S	8.197903e-03	mioa2421	4S	0.01
ncrb3077	4S	8.265993e-03	ncrc9517	4S	0.01
hfcr5737	4S	8.332211e-03	ncrl428	4S	0.01
seoa4070	4S	8.351138e-03	fcrc1758	4S	0.01
seob8065	4S	8.459463e-03	fcr0280	4S	0.01
ncrl631	4S	8.505128e-03	fcrb8901	4S	0.01
fcr0770	4S	8.634112e-03	mioa5231	4S	0.01
ncr2905	4S	8.640653e-03	seoc7281	4S	0.01
mioa6738	4S	8.769774e-03	fcrc1745	4S	0.01
miod1331	4S	8.912821e-03	miod0187	4S	0.01
mioa0707	4S	9.037843e-03	ncrb8790	4S	0.01
fcrb2299	4S	9.0502e-03	mioc7370	4S	0.01
seob3415	4S	9.05062e-03	miob4860	4S	0.01
seoa5933	4S	9.204501e-03	ncrc3258	4S	0.01
ncrc0101	4S	9.315893e-03	miob3411	4S	0.01
seob4140	4S	9.654697e-03	mioa3646	4S	0.01
mioa6035	4S	9.789009e-03	ncrc7085	4S	0.01
fcrb3466	4S	9.829055e-03	seoa0536	4S	0.01
mioc4366	4S	0.01	seob1783	4S	0.01
fcrb1787	4S	0.01	seoc3870	4S	0.01
seob3520	4S	0.01	fcrb7833	4S	0.01
fcr1068	4S	0.01	seob0418	4S	0.01
miob2743	4S	0.01	seoc0657	4S	0.01
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mioc3618	4S	0.01	mioa1062	4S	0.01
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ncrc3529	4S	0.01	ncrc9024	4S	0.01
seoc2670	4S	0.01	fcrb4294	4S	0.01
mioc6925	4S	0.01	seob2283	4S	0.01
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mioc2541	4S	0.01	fcrb7751	4S	0.01
miob8373	4S	0.01	fcrb1582	4S	0.01
seoa4460	4S	0.01	fcr7705	4S	0.01
miod6961	4S	0.01	ncr7876	4S	0.02
mioc0560	4S	0.01	seoa2962	4S	0.02

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seob1748	4S	0.04
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fcr6708	4S	0.04
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miob2668	4S	0.04	fcrb2556	4U	8.98e-04
fcr5930	4S	0.04	fcrb9420	4U	9.64e-04
fcr7518	4S	0.04	hfcr5381	4U	1.016874e-03
fcrb7880	4S	0.04	hfcr6406	4U	1.239885e-03
fcr3053	4S	0.04	miod1942	4U	1.305311e-03
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mioa8314	4S	0.04	miod6038	4U	1.395436e-03
seoa8921	4S	0.04	fcr3101	4U	1.487316e-03
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mioc7170	4U	2.53e-06	seoa9740	4U	1.598061e-03
mioa2072	4U	3.26e-06	mioa0494	4U	1.619093e-03
seoa4461	4U	5.29e-06	ncrc1367	4U	1.650171e-03
seoa6032	4U	5.48e-06	ncr5719	4U	1.677652e-03
seoa8894	4U	1.1e-05	seoa4305	4U	1.678116e-03
seob2697	4U	1.66e-05	seob0304	4U	1.693307e-03
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miod7421	4U	6.08e-05	fcrc5516	4U	1.799844e-03
seoa9373	4U	6.54e-05	seoc4380	4U	1.956915e-03
mioa1370	4U	8.87e-05	ncrc0150	4U	1.985831e-03
seoa9482	4U	9.27e-05	miod0340	4U	2.021229e-03
fcrb7339	4U	9.87e-05	miod2525	4U	2.174809e-03
fcr4477	4U	1.01e-04	fcrb2624	4U	2.174826e-03
fcrb0265	4U	1.2e-04	fcrb6187	4U	2.177878e-03
seob6189	4U	1.32e-04	fcr7419	4U	2.260166e-03
ncr3262	4U	1.4e-04	seoa1065	4U	2.312579e-03
fcr0253	4U	1.45e-04	fcrc6016	4U	2.3165e-03
seoa7652	4U	1.5e-04	miod6467	4U	2.34447e-03
seob6851	4U	1.55e-04	mioa1976	4U	2.452224e-03
fcrb3461	4U	1.6e-04	miob8143	4U	2.489145e-03
miod5651	4U	1.77e-04	seoa3670	4U	2.543649e-03
hfcr2390	4U	1.83e-04	ncrc1578	4U	2.579378e-03
miod5505	4U	1.89e-04	mioc8434	4U	2.661058e-03
seob6751	4U	2.02e-04	fcrb4409	4U	2.722505e-03
seoc2264	4U	2.1e-04	fcr0999	4U	2.730498e-03
fcrc1381	4U	2.28e-04	seob3307	4U	2.811695e-03
seoc1175	4U	2.33e-04	seoa9814	4U	2.836239e-03
seoc0999	4U	2.44e-04	mioa7140	4U	2.898369e-03
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mioc6260	4U	2.92e-04	miob0167	4U	2.975083e-03
fcrc0112	4U	3.06e-04	fcrb2933	4U	3.049655e-03
ncr0153	4U	3.07e-04	mioa2185	4U	3.147097e-03
fcr5779	4U	4.02e-04	mioa3856	4U	3.151528e-03
fcrb7830	4U	4.09e-04	seoa5683	4U	3.160612e-03
ncrc5663	4U	5.0e-04	mioa0187	4U	3.279663e-03
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seoa4739	4U	5.91e-04	miob8274	4U	3.404337e-03
seob9145	4U	6.11e-04	seob4972	4U	3.531512e-03
fcrc3750	4U	6.22e-04	seob2797	4U	3.6022e-03
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mioc4089	4U	7.46e-04	ncr2182	4U	3.847974e-03
mioc7362	4U	7.52e-04	seoa6573	4U	3.875968e-03
seob3303	4U	7.67e-04	ncrc4531	4U	4.208322e-03
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fcr0824	4U	8.62e-04	miob8226	4U	4.470203e-03
fcrc7102	4U	8.87e-04	fcrc0959	4U	4.530274e-03
mioa6731	4U	8.9e-04	mioa0890	4U	4.570501e-03

mioa0909	4U	4.589875e-03	fcrb3894	4U	9.03812e-03
miod4686	4U	4.657868e-03	fcrb2299	4U	9.0502e-03
ncrb4912	4U	4.752707e-03	seob3415	4U	9.05062e-03
mioa6739	4U	4.778158e-03	seoa1737	4U	9.470911e-03
mioa0826	4U	4.884238e-03	mioc4835	4U	9.495048e-03
mioa6621	4U	4.904983e-03	fcrc5846	4U	9.622113e-03
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fcrb8942	4U	5.08231e-03	mioa6035	4U	9.789009e-03
fcrc0430	4U	5.084925e-03	fcr3367	4U	9.80502e-03
ncr2862	4U	5.163569e-03	miob8214	4U	0.01
ncrc5500	4U	5.175143e-03	mioc4366	4U	0.01
ncr3313	4U	5.18529e-03	miob9336	4U	0.01
miod3592	4U	5.253602e-03	seob1574	4U	0.01
ncrb1398	4U	5.295501e-03	miob4037	4U	0.01
miod3254	4U	5.326719e-03	mioa2993	4U	0.01
mioc8619	4U	5.353299e-03	mioa6585	4U	0.01
fcr0990	4U	5.490991e-03	fcrb5527	4U	0.01
fcrc6560	4U	5.571911e-03	fcrb5918	4U	0.01
fcr3282	4U	5.608041e-03	ncrb8451	4U	0.01
seoc3588	4U	5.826485e-03	fcrb3584	4U	0.01
fcr5536	4U	6.049129e-03	fcrb5100	4U	0.01
ncrc0663	4U	6.085718e-03	hfcr2148	4U	0.01
fcr0608	4U	6.096137e-03	fcr2598	4U	0.01
ncrb1337	4U	6.21911e-03	mioa6135	4U	0.01
ncrc6712	4U	6.41394e-03	hfcr5970	4U	0.01
ncrc6000	4U	6.444479e-03	miod4464	4U	0.01
fcrb8187	4U	6.498087e-03	fcrb5389	4U	0.01
seob0703	4U	6.50097e-03	hfcr5237	4U	0.01
fcr4469	4U	6.567393e-03	fcrb5422	4U	0.01
mioa1303	4U	6.633139e-03	seoc2226	4U	0.01
fcrb2765	4U	6.689668e-03	mioa6721	4U	0.01
miod5612	4U	6.698915e-03	ncrc5959	4U	0.01
fcrb5087	4U	6.714694e-03	ncrc3529	4U	0.01
fcrb8536	4U	6.791086e-03	fcrb9481	4U	0.01
hfcr1760	4U	6.835569e-03	ncrc5653	4U	0.01
ncr6335	4U	6.907692e-03	seob1133	4U	0.01
miod3079	4U	6.91873e-03	miob0496	4U	0.01
ncr9956	4U	6.920421e-03	fcrb7588	4U	0.01
ncrb8207	4U	7.041692e-03	miob8373	4U	0.01
hfcr1914	4U	7.057729e-03	seoa4460	4U	0.01
mioa1427	4U	7.073426e-03	mioc0560	4U	0.01
seoa9935	4U	7.197022e-03	fcrb7808	4U	0.01
mioa6093	4U	7.268139e-03	mioa5097	4U	0.01
miod6213	4U	7.325332e-03	mioa2213	4U	0.01
miob4058	4U	7.329008e-03	miod4342	4U	0.01
seoa7078	4U	7.471779e-03	ncrc6171	4U	0.01
mioc6925	4U	7.512586e-03	seoa7094	4U	0.01
ncrc3936	4U	7.54805e-03	fcrb3897	4U	0.01
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ncrc6087	4U	7.662274e-03	seob0344	4U	0.01
hfcr0517	4U	7.704251e-03	seoa5552	4U	0.01
fcrb9655	4U	7.792172e-03	ncrb5737	4U	0.01
seoa0913	4U	7.91186e-03	fcrb5675	4U	0.01
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fcrb1329	4U	8.164602e-03	seoa2639	4U	0.01
miob1493	4U	8.197903e-03	seob7747	4U	0.01
fcrc0228	4U	8.284667e-03	miod2264	4U	0.01
seoa4070	4U	8.351138e-03	ncr1428	4U	0.01
fcrb1684	4U	8.355442e-03	fcrc1758	4U	0.01
seob8065	4U	8.459463e-03	mioa4944	4U	0.01
ncrc6264	4U	8.530558e-03	miob5119	4U	0.01
mioa6738	4U	8.769774e-03	seoc4748	4U	0.01
miob1506	4U	8.830271e-03	seob2938	4U	0.01
mioa0707	4U	9.037843e-03	fcrc1745	4U	0.01

miod0187	4U	0.01	mioa3940	4U	0.02
mioa8998	4U	0.01	seob9430	4U	0.02
mioc2039	4U	0.01	fcr6534	4U	0.02
mioc2546	4U	0.01	fcrb8901	4U	0.02
miob4860	4U	0.01	seob8873	4U	0.02
mioa9258	4U	0.01	miod6387	4U	0.02
ncrc3258	4U	0.01	miob3330	4U	0.02
miob3411	4U	0.01	fcrc5721	4U	0.02
ncrc7085	4U	0.01	hfcr2295	4U	0.02
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miob0973	4U	0.01	ncrb2798	4U	0.02
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seob0418	4U	0.01	seob4424	4U	0.02
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mioa0601	4U	0.01	miod6234	4U	0.03
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seob5465	4U	0.04	fcr1657	7A	6.595853e-03
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seob1155	4U	0.04	ncrc1469	7A	6.823212e-03
seoa3443	4U	0.04	fcrb3330	7A	6.930815e-03
ncrc4875	4U	0.04	seoa2391	7A	6.95326e-03
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seoc5285	4U	0.04	fcrb6472	7A	7.107374e-03
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miob9248	4U	0.04	ncrb0550	7A	7.225645e-03
fcr5930	4U	0.04	fcrb2754	7A	7.264187e-03
miod6058	4U	0.04	miob4956	7A	7.349209e-03
mioa8314	4U	0.04	seob6414	7A	7.368386e-03
seoa8921	4U	0.04	fcrb8485	7A	7.481387e-03
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fcrb4413	7A	1.011219e-03	mioc3523	7A	8.137321e-03
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miob8704	7A	1.816261e-03	mioc7471	7A	8.933176e-03
mioa8594	7A	2.071556e-03	ncrc8963	7A	9.097822e-03
seob8212	7A	2.146053e-03	ncrc1952	7A	9.151906e-03
fcrb5187	7A	2.160316e-03	mioa3428	7A	9.325496e-03
seob8321	7A	2.411238e-03	fcrb4400	7A	9.397631e-03
ncrb6087	7A	2.447161e-03	seoc3426	7A	9.422754e-03
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miob4574	7A	4.280838e-03	seoa5785	7A	0.01
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fcrc6470	7A	0.01	miob0167	7A	0.03
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seoc1230	7A	0.03	seob9302	7B	5.06e-04
seob5214	7A	0.03	ncr0836	7B	5.56e-04
seoc1661	7A	0.03	fcrb4413	7B	1.011219e-03
seob0497	7A	0.03	miob0636	7B	1.023089e-03
miob6373	7A	0.03	seoa5848	7B	1.02893e-03
ncr9934	7A	0.03	mioc7444	7B	1.056907e-03
miob6290	7A	0.03	fcrc2455	7B	1.247088e-03
mioa1276	7A	0.03	mioa9246	7B	1.742382e-03
mioa1165	7A	0.03	miob8704	7B	1.816261e-03
ncrc9681	7A	0.03	mioa8594	7B	2.071556e-03
ncrc4757	7A	0.03	seob8212	7B	2.146053e-03
fcrb9324	7A	0.03	fcrb5187	7B	2.160316e-03
seob3191	7A	0.04	seob8321	7B	2.411238e-03
seob6020	7A	0.04	ncrb6087	7B	2.447161e-03
mioa1353	7A	0.04	ncr9175	7B	2.614876e-03
mioc3716	7A	0.04	fcr3714	7B	2.947117e-03
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ncr7973	7A	0.04	hfcrc2295	7B	3.281442e-03
seoc0268	7A	0.04	seoc1664	7B	3.357752e-03
seob0047	7A	0.04	ncr0791	7B	3.83397e-03
seoa3633	7A	0.04	ncrc9642	7B	3.889141e-03
fcrb5092	7A	0.04	fcrb9096	7B	3.931911e-03
fcrb1687	7A	0.04	ncrc3049	7B	4.065059e-03
seob5064	7A	0.04	seob6535	7B	4.182541e-03
fcrb9520	7A	0.04	ncrc0729	7B	4.212215e-03
seob9946	7A	0.04	fcrc0075	7B	4.248397e-03
mioc3930	7A	0.04	miob4574	7B	4.280838e-03
seob1316	7A	0.04	seob5213	7B	4.291681e-03
ncr2256	7A	0.04	miod6560	7B	4.342561e-03
seoa6144	7A	0.04	hfcrc6611	7B	4.494123e-03
ncrc0592	7A	0.04	seoc1535	7B	4.804365e-03
miob2093	7A	0.04	seoc2510	7B	4.948173e-03
fcrb6734	7A	0.04	ncrb0513	7B	5.005288e-03
fcrb8910	7A	0.04	seoa8521	7B	5.057401e-03
seoa4158	7A	0.04	ncrc5150	7B	5.168054e-03
seoa6393	7A	0.04	fcrb1697	7B	5.247909e-03
miob4064	7A	0.04	ncrc9469	7B	5.631261e-03
mioc2694	7A	0.04	fcrb7944	7B	5.840758e-03

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seoa2391	7B	6.95326e-03	seoa3102	7B	0.01
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mioc8945	7B	0.04	ncrc5716	7C	6.68224e-03
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miob0180	7D	3.857035e-03
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miob0636	7D	4.169115e-03
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seob4451	7H	0.01	hfcr6498	7H	0.02
mioa6089	7H	0.01	hfcr8982	7H	0.02
fcrb1120	7H	0.01	miob6865	7H	0.02
hfcr5604	7H	0.01	ncr3435	7H	0.02
mioa5420	7H	0.01	ncrc4757	7H	0.02
mioa3654	7H	0.01	seoa1575	7H	0.02
hfcr6677	7H	0.01	seoa6521	7H	0.02
ncrc4597	7H	0.01	seoa9131	7H	0.02
seoa8921	7H	0.01	seob0572	7H	0.02
ncr7876	7H	0.01	seob5174	7H	0.02
seob0371	7H	0.01	seob6812	7H	0.02
fcrb3127	7H	0.01	seob7505	7H	0.02
hfcr9320	7H	0.01	ncrb4472	7H	0.02
seob5558	7H	0.02	ncr7136	7H	0.02
fcr3539	7H	0.02	seob4621	7H	0.02
seoa1582	7H	0.02	ncr0612	7H	0.02
seoa1118	7H	0.02	mioa3335	7H	0.02
ncr0851	7H	0.02	seoa0824	7H	0.02
fcrb2302	7H	0.02	ncr3149	7H	0.02
hfcr0366	7H	0.02	seob2108	7H	0.02
seoa0860	7H	0.02	fcrb3704	7H	0.02
fcr6412	7H	0.02	fcr7095	7H	0.02
fcrb1320	7H	0.02	ncr3827	7H	0.02
fcrb2596	7H	0.02	fcr5560	7H	0.02
fcrb4249	7H	0.02	seoa1611	7H	0.02
hfcr0041	7H	0.02	fcrb2933	7H	0.02
hfcr2295	7H	0.02	miob0682	7H	0.02
hfcr4488	7H	0.02	fcr0018	7H	0.02
hfcr6921	7H	0.02	fcr0796	7H	0.02
mioa1213	7H	0.02	fcr2160	7H	0.02
mioa2993	7H	0.02	fcr3701	7H	0.02
mioa4883	7H	0.02	fcr5220	7H	0.02
mioa5692	7H	0.02	fcr6161	7H	0.02
mioa5696	7H	0.02	fcrb3134	7H	0.02
mioa6064	7H	0.02	hfcr0023	7H	0.02
miob3794	7H	0.02	hfcr0383	7H	0.02
miob4248	7H	0.02	hfcr0776	7H	0.02
miob6878	7H	0.02	hfcr2803	7H	0.02
ncr2966	7H	0.02	hfcr3602	7H	0.02
ncr3163	7H	0.02	hfcr4444	7H	0.02
ncr4535	7H	0.02	hfcr5956	7H	0.02
seoa0099	7H	0.02	hfcr7151	7H	0.02
seoa1598	7H	0.02	hfcr7317	7H	0.02
seoa7647	7H	0.02	mioa0595	7H	0.02
seob1737	7H	0.02	mioa0884	7H	0.02
ncrc1103	7H	0.02	miob2645	7H	0.02
ncrc6348	7H	0.02	miob6562	7H	0.02
hfcr3956	7H	0.02	ncr0335	7H	0.02
seoa6573	7H	0.02	ncr2182	7H	0.02
hfcr0511	7H	0.02	ncr5264	7H	0.02
miob3042	7H	0.02	ncr7852	7H	0.02
ncr1550	7H	0.02	ncrb4441	7H	0.02
hfcr8540	7H	0.02	ncrc0139	7H	0.02

ncrc3464	7H	0.02
ncrc3650	7H	0.02
ncrc4994	7H	0.02
ncrc8841	7H	0.02
seoa0600	7H	0.02
seoa0956	7H	0.02
seoa1358	7H	0.02
seoa1875	7H	0.02
seoa2467	7H	0.02
seoa4012	7H	0.02
seoa5473	7H	0.02
seoa7295	7H	0.02
seoa7553	7H	0.02
seob0122	7H	0.02
seob3169	7H	0.02
seob5537	7H	0.02
hfcr8864	7H	0.02
seoa0549	7H	0.02
seob0688	7H	0.02
seoa1883	7H	0.02
fcr3549	7H	0.02
miob6437	7H	0.02
seob1853	7H	0.02
fcrb1017	7H	0.02
mioa4009	7H	0.02
mioa3672	7H	0.02
ncr0107	7H	0.02
fcrb2749	7H	0.02
seoa4783	7H	0.02
ncr0258	7H	0.02
seoa3408	7H	0.02
ncr0045	7H	0.02
seoa1765	7H	0.02
seoa5303	7H	0.02
ncrc5113	7H	0.02
ncrb5244	7H	0.02
seob7658	7H	0.02
miob4408	7H	0.02
hfcr1141	7H	0.03
seoa2135	7H	0.03
seoa2889	7H	0.03
fcr0837	7H	0.03
ncrc0320	7H	0.03
hfcr4114	7H	0.03
seob3545	7H	0.03
ncrc0529	7H	0.03
fcr7114	7H	0.03
seoa8300	7H	0.03
hfcr2390	7H	0.03
fcr2494	7H	0.03
fcrb2299	7H	0.03
fcrb2647	7H	0.03
fcrb3192	7H	0.03
fcrb4333	7H	0.03
fcrb5297	7H	0.03
hfcr1302	7H	0.03
hfcr3540	7H	0.03
mioa3812	7H	0.03
mioa3987	7H	0.03
mioa6913	7H	0.03
mioa9666	7H	0.03
miob2687	7H	0.03
ncr3148	7H	0.03
ncr4539	7H	0.03

ncr8542	7H	0.03
ncrb1956	7H	0.03
ncrc0583	7H	0.03
seoa0111	7H	0.03
seoa1102	7H	0.03
seoa6393	7H	0.03
seoa6612	7H	0.03
seoa6658	7H	0.03
seob6000	7H	0.03
seob6883	7H	0.03
seob7764	7H	0.03
ncrc0324	7H	0.03
fcr5958	7H	0.03
seob5726	7H	0.03
fcrb2396	7H	0.03
mioa8039	7H	0.03
fcrb3026	7H	0.03
seob0063	7H	0.03
mioa2522	7H	0.03
ncr3673	7H	0.03
fcr4566	7H	0.03
fcrb2041	7H	0.03
hfcr2941	7H	0.03
hfcr2963	7H	0.03
hfcr8804	7H	0.03
mioa1380	7H	0.03
mioa1947	7H	0.03
mioa4076	7H	0.03
mioa6772	7H	0.03
mioa9648	7H	0.03
ncr8337	7H	0.03
ncrb0200	7H	0.03
ncrb4437	7H	0.03
ncrb4555	7H	0.03
ncrc1380	7H	0.03
ncrc1595	7H	0.03
seoa1540	7H	0.03
seoa3109	7H	0.03
seoa9140	7H	0.03
seoa9930	7H	0.03
seob0386	7H	0.03
seob0442	7H	0.03
seob2011	7H	0.03
seob4466	7H	0.03
fcr0620	7H	0.03
miob6419	7H	0.03
fcr6142	7H	0.03
seoa0101	7H	0.03
mioa5329	7H	0.03
seoa0990	7H	0.03
miob2705	7H	0.03
ncr2176	7H	0.03
seoa1901	7H	0.03
hfcr3224	7H	0.03
ncrc9727	7H	0.03
seob3326	7H	0.03
hfcr5691	7H	0.03
ncrb4957	7H	0.03
ncrb8343	7H	0.03
seoa6661	7H	0.03
fcr7128	7H	0.03
mioa2536	7H	0.03
seob7444	7H	0.03
ncrb7376	7H	0.03

seoa1646	7H	0.03
ncrc1031	7H	0.03
seob2631	7H	0.03
fcrb2077	7H	0.03
seoa0044	7H	0.03
fcr0179	7H	0.03
fcr1242	7H	0.03
fcr2860	7H	0.03
fcrb1689	7H	0.03
fcrb5311	7H	0.03
hfcr5883	7H	0.03
mioa1971	7H	0.03
mioa7415	7H	0.03
miob0178	7H	0.03
miob1337	7H	0.03
miob2492	7H	0.03
miob2836	7H	0.03
miob4867	7H	0.03
ncr0019	7H	0.03
ncr3368	7H	0.03
ncr6619	7H	0.03
ncr7178	7H	0.03
ncrb1515	7H	0.03
ncrb6675	7H	0.03
ncrc0341	7H	0.03
ncrc0457	7H	0.03
ncrc3457	7H	0.03
ncrc4411	7H	0.03
ncrc8903	7H	0.03
seoa0003	7H	0.03
seoa0219	7H	0.03
seoa1900	7H	0.03
seoa3670	7H	0.03
seoa5302	7H	0.03
seob1410	7H	0.03
seob3119	7H	0.03
seob4440	7H	0.03
seob4965	7H	0.03
seob5684	7H	0.03
seob6630	7H	0.03
seob7744	7H	0.03
seob8287	7H	0.03
ncrc4362	7H	0.03
fcrb1687	7H	0.03
ncrc6417	7H	0.03
seob0376	7H	0.03
seob5711	7H	0.03
fcr4743	7H	0.03
fcr5472	7H	0.03
miob3120	7H	0.03
seoa4264	7H	0.04
mioa1062	7H	0.04
seoa7064	7H	0.04
seoa0840	7H	0.04
seoa6734	7H	0.04
ncr4416	7H	0.04
seob5493	7H	0.04
fcrb0624	7H	0.04
mioa6690	7H	0.04
mioa8713	7H	0.04
seob0763	7H	0.04
hfcr3019	7H	0.04
hfcr0750	7H	0.04
ncrc0292	7H	0.04

seoa0065	7H	0.04
hfcr2287	7H	0.04
seob6678	7H	0.04
seoa1232	7H	0.04
ncrc2776	7H	0.04
fcr5758	7H	0.04
ncrb3498	7H	0.04
seob4191	7H	0.04
seoa9935	7H	0.04
seoa1080	7H	0.04
fcrb3702	7H	0.04
fcr7146	7H	0.04
fcr1951	7H	0.04
fcr2167	7H	0.04
fcr2442	7H	0.04
fcr3983	7H	0.04
fcr4385	7H	0.04
fcr4927	7H	0.04
fcr7667	7H	0.04
fcrb2426	7H	0.04
fcrb2575	7H	0.04
hfcr5919	7H	0.04
hfcr7357	7H	0.04
hfcr9290	7H	0.04
hfcr9296	7H	0.04
mioa0245	7H	0.04
mioa3160	7H	0.04
miob1194	7H	0.04
miob6432	7H	0.04
ncr0266	7H	0.04
ncrb2558	7H	0.04
ncrb7726	7H	0.04
ncrc6423	7H	0.04
seoa4327	7H	0.04
seoa7249	7H	0.04
seoa9828	7H	0.04
seoa9998	7H	0.04
seob0999	7H	0.04
seob1008	7H	0.04
seob1052	7H	0.04
seob1426	7H	0.04
seob1842	7H	0.04
seob4570	7H	0.04
seob5441	7H	0.04
hfcr1697	7H	0.04
seoa0512	7H	0.04
seob2085	7H	0.04
seoa2449	7H	0.04
seob8241	7H	0.04
seoa0221	7H	0.04
seob4570	7H	0.04
fcr6887	7H	0.04
ncr7088	7H	0.04
seob1746	7H	0.04
hfcr8475	7H	0.04
ncrc5061	7H	0.04
ncr8843	7H	0.04
fcr0237	7H	0.04
seoa5698	7H	0.04
miob6228	7H	0.04
fcr5625	7H	0.04
fcrb2315	7H	0.04
hfcr0676	7H	0.04
hfcr2535	7H	0.04

hfcr5244	7H	0.04	fcrl2188	7I	5.437357e-03
hfcr5381	7H	0.04	miod3826	7I	6.215714e-03
hfcr6243	7H	0.04	seob0084	7I	6.215714e-03
hfcr6971	7H	0.04	seob0782	7I	6.215714e-03
hfcr7631	7H	0.04	seob4928	7I	6.215714e-03
hfcr9743	7H	0.04	seoa6178	7I	6.305954e-03
mioa0890	7H	0.04	seob2658	7I	7.212877e-03
mioa2295	7H	0.04	ncrc0749	7I	8.040483e-03
mioa4057	7H	0.04	ncrb8035	7I	8.36773e-03
mioa6595	7H	0.04	ncrc6774	7I	8.36773e-03
mioa7522	7H	0.04	seob4029	7I	8.879458e-03
mioa9062	7H	0.04	ncrc4302	7I	9.231614e-03
ncr1122	7H	0.04	ncr3397	7I	9.740651e-03
ncr2288	7H	0.04	seoa5698	7I	9.777088e-03
ncr3588	7H	0.04	mioc6341	7I	0.01
ncr4040	7H	0.04	miob9830	7I	0.01
ncr7097	7H	0.04	fcrb1158	7I	0.01
ncr8413	7H	0.04	fcrb6791	7I	0.01
ncr9587	7H	0.04	seoa5743	7I	0.01
ncrb7465	7H	0.04	seob1617	7I	0.01
ncrc1665	7H	0.04	fcr0187	7I	0.01
seoa1776	7H	0.04	fcrb5422	7I	0.01
seoa3287	7H	0.04	miod6554	7I	0.01
seoa6466	7H	0.04	ncrc9394	7I	0.01
seoa6637	7H	0.04	fcrc0350	7I	0.01
seoa6677	7H	0.04	ncr3587	7I	0.01
seoa6754	7H	0.04	seob5397	7I	0.01
seob0085	7H	0.04	fcr1394	7I	0.01
seob0755	7H	0.04	fcrb2996	7I	0.01
seob2067	7H	0.04	miob1833	7I	0.01
seob4333	7H	0.04	ncrc5706	7I	0.01
seob5336	7H	0.04	mioa0291	7I	0.01
hfcr8495	7H	0.04	fcr0535	7I	0.01
hfcr3846	7H	0.04	fcrb2715	7I	0.01
seoa1483	7H	0.04	ncrb8160	7I	0.01
seoa9603	7H	0.04	ncrc3864	7I	0.01
mioa9179	7H	0.04	ncrd4954	7I	0.01
seoa3344	7H	0.04	seoa9930	7I	0.01
mioa8861	7H	0.04	seob0928	7I	0.02
ncrc5054	7H	0.04	mioc7509	7I	0.02
hfcr6534	7H	0.04	cr0491	7I	0.02
seob6368	7H	0.04	seob9435	7I	0.02
mioa8594	7H	0.04	mioc6973	7I	0.02
fcrb2545	7H	0.04	ncrd7372	7I	0.02
seoa0799	7H	0.04	ncr0004	7I	0.02
miob5632	7H	0.04	seoc1305	7I	0.02
mioa4014	7H	0.04	seob9614	7I	0.02
miob3911	7I	4.41e-04	ncrd4929	7I	0.02
seob2067	7I	6.57e-04	fcrb1769	7I	0.02
ncrc4772	7I	8.82e-04	fcrb5441	7I	0.02
seoc0149	7I	2.085221e-03	fcrb6469	7I	0.02
ncrc4759	7I	2.552738e-03	fcrb9124	7I	0.02
ncrb0074	7I	2.926149e-03	miod4539	7I	0.02
fcrb9565	7I	3.208495e-03	ncr7852	7I	0.02
fcrc2431	7I	3.223683e-03	ncrc4132	7I	0.02
hfcr1826	7I	3.257445e-03	ncrc6749	7I	0.02
miob3120	7I	3.257445e-03	seoa8979	7I	0.02
seoa9209	7I	3.257445e-03	seoc1025	7I	0.02
soa0550	7I	4.178366e-03	seoa2381	7I	0.02
miod6038	7I	4.186981e-03	ncrc9168	7I	0.02
ncrc3690	7I	4.482529e-03	fcrb8664	7I	0.02
fcrb4718	7I	4.540706e-03	ncr1122	7I	0.02
seoa9656	7I	4.540706e-03	miod2330	7I	0.02
mioc6269	7I	5.370316e-03	ncrb6846	7I	0.02

ncr9105	7I	0.02
fcr2498	7I	0.02
hfcr0130	7I	0.02
miob4221	7I	0.02
mioc8254	7I	0.02
fcrc6010	7I	0.02
fcr1225	7I	0.02
fcr1994	7I	0.02
fcrb7723	7I	0.02
mioa4810	7I	0.02
miob5412	7I	0.02
mioc3574	7I	0.02
ncrc0320	7I	0.02
ncrc5762	7I	0.02
ncrd3638	7I	0.03
fcrb4383	7I	0.03
fcrb7699	7I	0.03
fcrb3153	7I	0.03
ncrb3468	7I	0.03
fcrc5506	7I	0.03
seob7082	7I	0.03
miob8992	7I	0.03
fcrc7243	7I	0.03
hfcr3019	7I	0.03
ncrd3708	7I	0.03
seoa1776	7I	0.03
seoa1883	7I	0.03
seoa5580	7I	0.03

seoc2136	7I	0.03
miob9533	7I	0.03
fcrb6738	7I	0.03
fcr4725	7I	0.04
fcrb8236	7I	0.04
fcrb6723	7I	0.04
fcr1463	7I	0.04
miob8694	7I	0.04
seoa7917	7I	0.04
ncrc9530	7I	0.04
seob6558	7I	0.04
mioa5468	7I	0.04
miod6324	7I	0.04
fcrb0131	7I	0.04
fcrc0839	7I	0.04
hfcr6336	7I	0.04
mioa5202	7I	0.04
ncr7668	7I	0.04
ncrc5492	7I	0.04
seob4065	7I	0.04
seob9420	7I	0.04
seob9818	7I	0.04
seoc4748	7I	0.04
hfcr2275	7I	0.04
seoa8018	7I	0.04
ncrc0728	7I	0.04
fcrb3080	7I	0.04



Table #8B

AffySpot	Table#	pvalue
201794_s_at	1AA	1.68e-06
212640_at	1AA	4.74e-06
205060_at	1AA	4.18e-05
204686_at	1AA	6.09e-05
212648_at	1AA	6.57e-05
224369_s_at	1AA	6.68e-05
221306_at	1AA	1.23e-04
224906_at	1AA	1.35e-04
203810_at	1AA	1.37e-04
208248_x_at	1AA	1.67e-04
221582_at	1AA	1.85e-04
216907_x_at	1AA	1.92e-04
211935_at	1AA	2.21e-04
212718_at	1AA	2.37e-04
203254_s_at	1AA	2.53e-04
215049_x_at	1AA	2.69e-04
202443_x_at	1AA	2.69e-04
208772_at	1AA	2.69e-04
214173_x_at	1AA	2.72e-04
230243_at	1AA	2.91e-04
201935_s_at	1AA	3.21e-04
224859_at	1AA	3.63e-04
206059_at	1AA	3.84e-04
204573_at	1AA	4.09e-04
218236_s_at	1AA	4.12e-04
200709_at	1AA	4.2e-04
202783_at	1AA	4.24e-04
203037_s_at	1AA	4.3e-04
206632_s_at	1AA	4.35e-04
1564785_at	1AA	4.37e-04
200697_at	1AA	4.56e-04
202638_s_at	1AA	4.65e-04
202786_at	1AA	4.73e-04
208704_x_at	1AA	4.78e-04
212863_x_at	1AA	4.91e-04
213906_at	1AA	4.93e-04
209585_s_at	1AA	5.43e-04
203392_s_at	1AA	5.55e-04
41577_at	1AA	6.09e-04
202471_s_at	1AA	6.18e-04
202610_s_at	1AA	6.26e-04
200046_at	1AA	6.37e-04
200742_s_at	1AA	6.39e-04
204497_at	1AA	6.55e-04
204396_s_at	1AA	6.59e-04
203970_s_at	1AA	6.62e-04
201118_at	1AA	6.72e-04
201687_s_at	1AA	6.86e-04
209960_at	1AA	7.13e-04
212500_at	1AA	7.33e-04
217862_at	1AA	7.33e-04
217970_s_at	1AA	7.43e-04
204806_x_at	1AA	7.43e-04
203264_s_at	1AA	7.48e-04
219183_s_at	1AA	7.53e-04
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202096_s_at	1AA	7.86e-04
202720_at	1AA	7.88e-04
217197_x_at	1AA	8.02e-04

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91684_g_at	1AA	8.64e-04
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200867_at	1AA	8.76e-04
202545_at	1AA	8.9e-04
207314_x_at	1AA	8.9e-04
211733_x_at	1AA	9.02e-04
202184_s_at	1AA	9.34e-04
214109_at	1AA	9.39e-04
214743_at	1AA	9.48e-04
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211926_s_at	1AA	9.48e-04
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223217_s_at	1AE	1.175873e-03	211537_x_at	1AE	6.620416e-03
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200950_at	1S	1.25621e-04
200881_s_at	1S	1.25621e-04
201912_s_at	1S	1.25621e-04
201995_at	1S	1.25621e-04
200961_at	1S	1.25621e-04
200920_s_at	1S	1.25621e-04
200914_x_at	1S	1.25621e-04
201925_s_at	1S	1.25621e-04
200985_s_at	1S	1.25621e-04
201985_at	1S	1.25621e-04
201944_at	1S	1.25621e-04
200007_at	1S	1.26e-04
200654_at	1S	1.28e-04
219460_s_at	1S	1.28328e-04
218981_at	1S	1.28328e-04
212747_at	1S	1.28328e-04
213012_at	1S	1.28328e-04
216268_s_at	1S	1.28328e-04
203598_s_at	1S	1.28328e-04
204478_s_at	1S	1.28328e-04
204565_at	1S	1.28328e-04
204214_s_at	1S	1.28328e-04
204554_at	1S	1.28328e-04
211297_s_at	1S	1.28328e-04
210004_at	1S	1.28328e-04
203116_s_at	1S	1.28328e-04
202948_at	1S	1.28328e-04
202589_at	1S	1.28328e-04
206440_at	1S	1.28328e-04
206995_x_at	1S	1.28328e-04
209099_x_at	1S	1.28328e-04
208886_at	1S	1.28328e-04
206621_s_at	1S	1.29e-04
201859_at	1S	1.29e-04
208442_s_at	1S	1.31e-04
218498_s_at	1S	1.31689e-04
218578_at	1S	1.31689e-04
219551_at	1S	1.31689e-04
212312_at	1S	1.31689e-04
216903_s_at	1S	1.31689e-04
209667_at	1S	1.31689e-04
202349_at	1S	1.31689e-04
203097_s_at	1S	1.32e-04
213554_s_at	1S	1.33e-04
206209_s_at	1S	1.33e-04
225884_s_at	1S	1.34e-04
200657_at	1S	1.34e-04
212264_s_at	1S	1.35e-04
216295_s_at	1S	1.35e-04
219016_at	1S	1.35933e-04
203912_s_at	1S	1.35933e-04
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206676_at	1S	1.35933e-04
206157_at	1S	1.35933e-04
215051_x_at	1S	1.37e-04
200068_s_at	1S	1.38e-04
210453_x_at	1S	1.4e-04
219403_s_at	1S	1.41397e-04
213515_x_at	1S	1.41397e-04
221490_at	1S	1.41397e-04
221504_s_at	1S	1.41397e-04

210254_at	1S	1.41397e-04
210244_at	1S	1.41397e-04
209273_s_at	1S	1.41397e-04
201161_s_at	1S	1.41397e-04
200857_s_at	1S	1.42e-04
201441_at	1S	1.42e-04
217865_at	1S	1.43e-04
200660_at	1S	1.43e-04
212519_at	1S	1.44e-04
206464_at	1S	1.44e-04
201652_at	1S	1.44e-04
200046_at	1S	1.46e-04
216274_s_at	1S	1.47e-04
219445_at	1S	1.48601e-04
219129_s_at	1S	1.48601e-04
213173_at	1S	1.48601e-04
209211_at	1S	1.48601e-04
207988_s_at	1S	1.49e-04
200001_at	1S	1.49e-04
217768_at	1S	1.5e-04
200971_s_at	1S	1.53e-04
213151_s_at	1S	1.54e-04
215832_x_at	1S	1.55e-04
203538_at	1S	1.57e-04
200055_at	1S	1.57e-04
203254_s_at	1S	1.58e-04
202961_s_at	1S	1.58e-04
208948_s_at	1S	1.58e-04
215047_at	1S	1.5837e-04
213440_at	1S	1.5837e-04
204614_at	1S	1.5837e-04
209773_s_at	1S	1.5837e-04
200932_s_at	1S	1.5837e-04
218352_at	1S	1.62e-04
205335_s_at	1S	1.62e-04
210389_x_at	1S	1.63e-04
203011_at	1S	1.63e-04
214315_x_at	1S	1.64e-04
202325_s_at	1S	1.64e-04
205756_s_at	1S	1.64e-04
204093_at	1S	1.66e-04
227467_at	1S	1.67e-04
220467_at	1S	1.71e-04
211270_x_at	1S	1.71e-04
219384_s_at	1S	1.72083e-04
218992_at	1S	1.72083e-04
204218_at	1S	1.72083e-04
204419_x_at	1S	1.72083e-04
209892_at	1S	1.72083e-04
212267_at	1S	1.74e-04
202187_s_at	1S	1.74e-04
235683_at	1S	1.75e-04
214430_at	1S	1.75e-04
200019_s_at	1S	1.75e-04
227207_x_at	1S	1.76e-04
202859_x_at	1S	1.76e-04
53912_at	1S	1.77e-04
201954_at	1S	1.78e-04
208818_s_at	1S	1.79e-04
209499_x_at	1S	1.82e-04
204340_at	1S	1.88e-04
202801_at	1S	1.89e-04
218904_s_at	1S	1.92183e-04
212458_at	1S	1.92183e-04

202946_s_at	1S	1.92183e-04
202252_at	1S	1.92183e-04
200876_s_at	1S	1.94e-04
201118_at	1S	1.95e-04
203133_at	1S	1.96e-04
203332_s_at	1S	1.97e-04
203508_at	1S	2.0e-04
209791_at	1S	2.01e-04
234631_at	1S	2.04e-04
219731_at	1S	2.04e-04
36019_at	1S	2.05329e-04
34408_at	1S	2.05329e-04
266_s_at	1S	2.05329e-04
34210_at	1S	2.05329e-04
46270_at	1S	2.05329e-04
218482_at	1S	2.05329e-04
218662_s_at	1S	2.05329e-04
218583_s_at	1S	2.05329e-04
218487_at	1S	2.05329e-04
218883_s_at	1S	2.05329e-04
218582_at	1S	2.05329e-04
219571_s_at	1S	2.05329e-04
218616_at	1S	2.05329e-04
220367_s_at	1S	2.05329e-04
218739_at	1S	2.05329e-04
218871_x_at	1S	2.05329e-04
214953_s_at	1S	2.05329e-04
213229_at	1S	2.05329e-04
212830_at	1S	2.05329e-04
214531_s_at	1S	2.05329e-04
212449_s_at	1S	2.05329e-04
213911_s_at	1S	2.05329e-04
212602_at	1S	2.05329e-04
213154_s_at	1S	2.05329e-04
212638_s_at	1S	2.05329e-04
214938_x_at	1S	2.05329e-04
214590_s_at	1S	2.05329e-04
213011_s_at	1S	2.05329e-04
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217986_s_at	1S	2.05329e-04
217898_at	1S	2.05329e-04
218171_at	1S	2.05329e-04
218310_at	1S	2.05329e-04
217827_s_at	1S	2.05329e-04
215933_s_at	1S	2.05329e-04
218348_s_at	1S	2.05329e-04
218107_at	1S	2.05329e-04
218313_s_at	1S	2.05329e-04
215127_s_at	1S	2.05329e-04
218163_at	1S	2.05329e-04
218357_s_at	1S	2.05329e-04
216383_at	1S	2.05329e-04
218251_at	1S	2.05329e-04
218254_s_at	1S	2.05329e-04
215498_s_at	1S	2.05329e-04
203286_at	1S	2.05329e-04
204362_at	1S	2.05329e-04
203457_at	1S	2.05329e-04
204026_s_at	1S	2.05329e-04
203266_s_at	1S	2.05329e-04
203748_x_at	1S	2.05329e-04
203690_at	1S	2.05329e-04
203739_at	1S	2.05329e-04
221188_s_at	1S	2.05329e-04

221002_s_at	1S	2.05329e-04	201275_at	1S	2.05329e-04
222235_s_at	1S	2.05329e-04	201303_at	1S	2.05329e-04
220940_at	1S	2.05329e-04	201811_x_at	1S	2.05329e-04
220615_s_at	1S	2.05329e-04	201470_at	1S	2.05329e-04
220603_s_at	1S	2.05329e-04	201336_at	1S	2.05329e-04
221478_at	1S	2.05329e-04	201238_s_at	1S	2.05329e-04
221479_s_at	1S	2.05329e-04	201096_s_at	1S	2.05329e-04
209515_s_at	1S	2.05329e-04	200861_at	1S	2.05329e-04
211015_s_at	1S	2.05329e-04	201298_s_at	1S	2.05329e-04
211657_at	1S	2.05329e-04	201328_at	1S	2.05329e-04
211383_s_at	1S	2.05329e-04	201312_s_at	1S	2.05329e-04
210142_x_at	1S	2.05329e-04	201695_s_at	1S	2.05329e-04
210153_s_at	1S	2.05329e-04	201256_at	1S	2.05329e-04
212204_at	1S	2.05329e-04	201192_s_at	1S	2.05329e-04
209678_s_at	1S	2.05329e-04	213646_x_at	1S	2.06e-04
210639_s_at	1S	2.05329e-04	207585_s_at	1S	2.08e-04
209919_x_at	1S	2.05329e-04	202189_x_at	1S	2.14e-04
209734_at	1S	2.05329e-04	200966_x_at	1S	2.14e-04
212240_s_at	1S	2.05329e-04	201400_at	1S	2.14e-04
202243_s_at	1S	2.05329e-04	220122_at	1S	2.15e-04
202725_at	1S	2.05329e-04	222625_s_at	1S	2.15e-04
202499_s_at	1S	2.05329e-04	202090_s_at	1S	2.16e-04
202026_at	1S	2.05329e-04	200008_s_at	1S	2.16e-04
202788_at	1S	2.05329e-04	224707_at	1S	2.17e-04
203232_s_at	1S	2.05329e-04	213571_s_at	1S	2.17e-04
203042_at	1S	2.05329e-04	51146_at	1S	2.17434e-04
202313_at	1S	2.05329e-04	213159_at	1S	2.17434e-04
202206_at	1S	2.05329e-04	212024_x_at	1S	2.17434e-04
203127_s_at	1S	2.05329e-04	210088_x_at	1S	2.17434e-04
202872_at	1S	2.05329e-04	203203_s_at	1S	2.17434e-04
202535_at	1S	2.05329e-04	207269_at	1S	2.17434e-04
203021_at	1S	2.05329e-04	200678_x_at	1S	2.19e-04
202511_s_at	1S	2.05329e-04	200043_at	1S	2.19e-04
202878_s_at	1S	2.05329e-04	224564_s_at	1S	2.2e-04
202464_s_at	1S	2.05329e-04	208319_s_at	1S	2.2e-04
205550_s_at	1S	2.05329e-04	200893_at	1S	2.2e-04
205896_at	1S	2.05329e-04	214882_s_at	1S	2.21e-04
207266_x_at	1S	2.05329e-04	201980_s_at	1S	2.22e-04
207186_s_at	1S	2.05329e-04	201338_x_at	1S	2.22e-04
206158_s_at	1S	2.05329e-04	204393_s_at	1S	2.23311e-04
206522_at	1S	2.05329e-04	211072_x_at	1S	2.26e-04
207655_s_at	1S	2.05329e-04	221741_s_at	1S	2.29e-04
208770_s_at	1S	2.05329e-04	218806_s_at	1S	2.32466e-04
208749_x_at	1S	2.05329e-04	204157_s_at	1S	2.32466e-04
209216_at	1S	2.05329e-04	207335_x_at	1S	2.33e-04
209141_at	1S	2.05329e-04	202096_s_at	1S	2.34e-04
208949_s_at	1S	2.05329e-04	203667_at	1S	2.38e-04
208864_s_at	1S	2.05329e-04	206834_at	1S	2.4e-04
208785_s_at	1S	2.05329e-04	200037_s_at	1S	2.4e-04
207980_s_at	1S	2.05329e-04	218387_s_at	1S	2.41e-04
209249_s_at	1S	2.05329e-04	208248_x_at	1S	2.41e-04
207805_s_at	1S	2.05329e-04	200772_x_at	1S	2.41e-04
209206_at	1S	2.05329e-04	208308_s_at	1S	2.42e-04
208579_x_at	1S	2.05329e-04	202591_s_at	1S	2.45e-04
208704_x_at	1S	2.05329e-04	201724_s_at	1S	2.45e-04
208898_at	1S	2.05329e-04	203922_s_at	1S	2.49e-04
209311_at	1S	2.05329e-04	217720_at	1S	2.5e-04
200734_s_at	1S	2.05329e-04	207508_at	1S	2.5e-04
200853_at	1S	2.05329e-04	208634_s_at	1S	2.51e-04
200800_s_at	1S	2.05329e-04	203943_at	1S	2.54e-04
200746_s_at	1S	2.05329e-04	206245_s_at	1S	2.55e-04
200063_s_at	1S	2.05329e-04	201588_at	1S	2.57e-04
200863_s_at	1S	2.05329e-04	1552773_at	1S	2.59e-04
201352_at	1S	2.05329e-04	201105_at	1S	2.59e-04

AFFX-HUMGAPDH/			212323_s_at	1S	3.25715e-04
M33197	1S	2.6e-04	213501_at	1S	3.25715e-04
212869_x_at	1S	2.6e-04	213624_at	1S	3.25715e-04
217801_at	1S	2.63e-04	212527_at	1S	3.25715e-04
216993_s_at	1S	2.64e-04	213988_s_at	1S	3.25715e-04
214501_s_at	1S	2.69e-04	218196_at	1S	3.25715e-04
203137_at	1S	2.69e-04	218271_s_at	1S	3.25715e-04
208517_x_at	1S	2.7e-04	217843_s_at	1S	3.25715e-04
217547_x_at	1S	2.71e-04	217707_x_at	1S	3.25715e-04
205292_s_at	1S	2.71e-04	217835_x_at	1S	3.25715e-04
204789_at	1S	2.73e-04	217728_at	1S	3.25715e-04
218872_at	1S	2.75101e-04	217862_at	1S	3.25715e-04
202080_s_at	1S	2.75101e-04	216457_s_at	1S	3.25715e-04
206116_s_at	1S	2.75101e-04	218189_s_at	1S	3.25715e-04
221425_s_at	1S	2.76199e-04	218209_s_at	1S	3.25715e-04
202947_s_at	1S	2.76199e-04	218252_at	1S	3.25715e-04
201573_s_at	1S	2.76199e-04	218101_s_at	1S	3.25715e-04
218190_s_at	1S	2.86e-04	217885_at	1S	3.25715e-04
203370_s_at	1S	2.88e-04	218208_at	1S	3.25715e-04
220980_s_at	1S	2.89e-04	217552_x_at	1S	3.25715e-04
71933_at	1S	2.94e-04	204219_s_at	1S	3.25715e-04
203471_s_at	1S	2.94e-04	203656_at	1S	3.25715e-04
203583_at	1S	2.94e-04	203408_s_at	1S	3.25715e-04
200651_at	1S	2.95e-04	204079_at	1S	3.25715e-04
217958_at	1S	2.97e-04	203487_s_at	1S	3.25715e-04
200777_s_at	1S	2.99e-04	204028_s_at	1S	3.25715e-04
212130_x_at	1S	3.0e-04	204297_at	1S	3.25715e-04
209476_at	1S	3.02e-04	203321_s_at	1S	3.25715e-04
217724_at	1S	3.05e-04	203655_at	1S	3.25715e-04
205033_s_at	1S	3.06e-04	203605_at	1S	3.25715e-04
210371_s_at	1S	3.07e-04	203544_s_at	1S	3.25715e-04
64408_s_at	1S	3.0913e-04	203775_at	1S	3.25715e-04
218833_at	1S	3.0913e-04	203284_s_at	1S	3.25715e-04
220000_at	1S	3.0913e-04	203279_at	1S	3.25715e-04
205557_at	1S	3.0913e-04	203501_at	1S	3.25715e-04
206364_at	1S	3.0913e-04	221485_at	1S	3.25715e-04
201216_at	1S	3.17e-04	221724_s_at	1S	3.25715e-04
225210_s_at	1S	3.2e-04	221058_s_at	1S	3.25715e-04
200083_at	1S	3.21e-04	221620_s_at	1S	3.25715e-04
209685_s_at	1S	3.22e-04	220926_s_at	1S	3.25715e-04
201499_s_at	1S	3.23e-04	221613_s_at	1S	3.25715e-04
45526_g_at	1S	3.25715e-04	221452_s_at	1S	3.25715e-04
218668_s_at	1S	3.25715e-04	221011_s_at	1S	3.25715e-04
219492_at	1S	3.25715e-04	221257_x_at	1S	3.25715e-04
219816_s_at	1S	3.25715e-04	209551_at	1S	3.25715e-04
219449_s_at	1S	3.25715e-04	209619_at	1S	3.25715e-04
219649_at	1S	3.25715e-04	211684_s_at	1S	3.25715e-04
218718_at	1S	3.25715e-04	209452_s_at	1S	3.25715e-04
219359_at	1S	3.25715e-04	210395_x_at	1S	3.25715e-04
219938_s_at	1S	3.25715e-04	209640_at	1S	3.25715e-04
220305_at	1S	3.25715e-04	209512_at	1S	3.25715e-04
218660_at	1S	3.25715e-04	209513_s_at	1S	3.25715e-04
218949_s_at	1S	3.25715e-04	210951_x_at	1S	3.25715e-04
212610_at	1S	3.25715e-04	210119_at	1S	3.25715e-04
212982_at	1S	3.25715e-04	209517_s_at	1S	3.25715e-04
212273_x_at	1S	3.25715e-04	209882_at	1S	3.25715e-04
212807_s_at	1S	3.25715e-04	203184_at	1S	3.25715e-04
212973_at	1S	3.25715e-04	202671_s_at	1S	3.25715e-04
214198_s_at	1S	3.25715e-04	202364_at	1S	3.25715e-04
214352_s_at	1S	3.25715e-04	202939_at	1S	3.25715e-04
213532_at	1S	3.25715e-04	203126_at	1S	3.25715e-04
212369_at	1S	3.25715e-04	202343_x_at	1S	3.25715e-04
212572_at	1S	3.25715e-04	203044_at	1S	3.25715e-04
212685_s_at	1S	3.25715e-04	202727_s_at	1S	3.25715e-04



202824_s_at	1S	3.25715e-04
202010_s_at	1S	3.25715e-04
202534_x_at	1S	3.25715e-04
202269_x_at	1S	3.25715e-04
202845_s_at	1S	3.25715e-04
202603_at	1S	3.25715e-04
202105_at	1S	3.25715e-04
202297_s_at	1S	3.25715e-04
202432_at	1S	3.25715e-04
202100_at	1S	3.25715e-04
203090_at	1S	3.25715e-04
203243_s_at	1S	3.25715e-04
206200_s_at	1S	3.25715e-04
205740_s_at	1S	3.25715e-04
207332_s_at	1S	3.25715e-04
207387_s_at	1S	3.25715e-04
205403_at	1S	3.25715e-04
205349_at	1S	3.25715e-04
208924_at	1S	3.25715e-04
208923_at	1S	3.25715e-04
209251_x_at	1S	3.25715e-04
207616_s_at	1S	3.25715e-04
209276_s_at	1S	3.25715e-04
209194_at	1S	3.25715e-04
208640_at	1S	3.25715e-04
209027_s_at	1S	3.25715e-04
208882_s_at	1S	3.25715e-04
200829_x_at	1S	3.25715e-04
200634_at	1S	3.25715e-04
200839_s_at	1S	3.25715e-04
200625_s_at	1S	3.25715e-04
200728_at	1S	3.25715e-04
200614_at	1S	3.25715e-04
201007_at	1S	3.25715e-04
200889_s_at	1S	3.25715e-04
201643_x_at	1S	3.25715e-04
201725_at	1S	3.25715e-04
201642_at	1S	3.25715e-04
201670_s_at	1S	3.25715e-04
201359_at	1S	3.25715e-04
201493_s_at	1S	3.25715e-04
201163_s_at	1S	3.25715e-04
201593_s_at	1S	3.25715e-04
201091_s_at	1S	3.25715e-04
201483_s_at	1S	3.25715e-04
200980_s_at	1S	3.25715e-04
201097_s_at	1S	3.25715e-04
201277_s_at	1S	3.25715e-04
201817_at	1S	3.25715e-04
201200_at	1S	3.25715e-04
201903_at	1S	3.25715e-04
201186_at	1S	3.25715e-04
201487_at	1S	3.25715e-04
201807_at	1S	3.25715e-04
213867_x_at	1S	3.26e-04
212740_at	1S	3.28e-04
211746_x_at	1S	3.32e-04
201687_s_at	1S	3.32e-04
210739_x_at	1S	3.39e-04
218334_at	1S	3.41e-04
217845_x_at	1S	3.42e-04
216526_x_at	1S	3.43e-04
214467_at	1S	3.45e-04
204509_at	1S	3.47e-04

200780_x_at	1S	3.52e-04
212531_at	1S	3.54546e-04
207384_at	1S	3.55e-04
219607_s_at	1S	3.55624e-04
219700_at	1S	3.55624e-04
219292_at	1S	3.55624e-04
212683_at	1S	3.55624e-04
214620_x_at	1S	3.55624e-04
203744_at	1S	3.55624e-04
209498_at	1S	3.55624e-04
209916_at	1S	3.55624e-04
209339_at	1S	3.55624e-04
201930_at	1S	3.55624e-04
204480_s_at	1S	3.57e-04
217954_s_at	1S	3.64e-04
208698_s_at	1S	3.68e-04
203104_at	1S	3.71e-04
207974_s_at	1S	3.72e-04
201443_s_at	1S	3.75e-04
204249_s_at	1S	3.81e-04
207320_x_at	1S	3.81e-04
206687_s_at	1S	3.81e-04
218280_x_at	1S	3.85e-04
202546_at	1S	3.87e-04
218603_at	1S	3.9e-04
211749_s_at	1S	3.9e-04
200941_at	1S	3.9e-04
200990_at	1S	3.92e-04
219326_s_at	1S	3.93443e-04
214523_at	1S	3.93443e-04
208873_s_at	1S	3.96e-04
202315_s_at	1S	3.97e-04
213526_s_at	1S	3.98e-04
212780_at	1S	3.99e-04
217773_s_at	1S	4.0e-04
202471_s_at	1S	4.0e-04
31826_at	1S	4.07e-04
200848_at	1S	4.08e-04
208669_s_at	1S	4.1e-04
202469_s_at	1S	4.11e-04
203788_s_at	1S	4.13e-04
221816_s_at	1S	4.16e-04
202173_s_at	1S	4.17e-04
200097_s_at	1S	4.18e-04
221474_at	1S	4.25e-04
202581_at	1S	4.25e-04
209384_at	1S	4.25e-04
200073_s_at	1S	4.31e-04
210840_s_at	1S	4.36e-04
33323_r_at	1S	4.37e-04
214733_s_at	1S	4.42332e-04
217427_s_at	1S	4.42332e-04
211271_x_at	1S	4.46e-04
214435_x_at	1S	4.47e-04
212697_at	1S	4.5e-04
204605_at	1S	4.52e-04
212584_at	1S	4.57e-04
216221_s_at	1S	4.6e-04
200964_at	1S	4.61e-04
213318_s_at	1S	4.65e-04
AFFX-HUMGAPDH/		
M33197	1S	4.67e-04
218364_at	1S	4.67e-04
201322_at	1S	4.69e-04

207507_s_at	1S	4.71e-04	202636_at	1S	5.02887e-04
37232_at	1S	4.72e-04	202770_s_at	1S	5.02887e-04
202118_s_at	1S	4.78e-04	202956_at	1S	5.02887e-04
216210_x_at	1S	4.87e-04	202304_at	1S	5.02887e-04
217356_s_at	1S	4.88e-04	202811_at	1S	5.02887e-04
205882_x_at	1S	4.88e-04	202506_at	1S	5.02887e-04
203630_s_at	1S	4.9e-04	202568_s_at	1S	5.02887e-04
217794_at	1S	4.91e-04	202430_s_at	1S	5.02887e-04
209187_at	1S	4.91e-04	207168_s_at	1S	5.02887e-04
221222_s_at	1S	4.99e-04	205575_at	1S	5.02887e-04
224690_at	1S	5.0e-04	205842_s_at	1S	5.02887e-04
44696_at	1S	5.02887e-04	206618_at	1S	5.02887e-04
219620_x_at	1S	5.02887e-04	205027_s_at	1S	5.02887e-04
218854_at	1S	5.02887e-04	205513_at	1S	5.02887e-04
219104_at	1S	5.02887e-04	206150_at	1S	5.02887e-04
219132_at	1S	5.02887e-04	205607_s_at	1S	5.02887e-04
218738_s_at	1S	5.02887e-04	209295_at	1S	5.02887e-04
218764_at	1S	5.02887e-04	208284_x_at	1S	5.02887e-04
212265_at	1S	5.02887e-04	208540_x_at	1S	5.02887e-04
212916_at	1S	5.02887e-04	208709_s_at	1S	5.02887e-04
212717_at	1S	5.02887e-04	209281_s_at	1S	5.02887e-04
213095_x_at	1S	5.02887e-04	209020_at	1S	5.02887e-04
212674_s_at	1S	5.02887e-04	208919_s_at	1S	5.02887e-04
213923_at	1S	5.02887e-04	208615_s_at	1S	5.02887e-04
213918_s_at	1S	5.02887e-04	208310_s_at	1S	5.02887e-04
218113_at	1S	5.02887e-04	208091_s_at	1S	5.02887e-04
218472_s_at	1S	5.02887e-04	200621_at	1S	5.02887e-04
215424_s_at	1S	5.02887e-04	200619_at	1S	5.02887e-04
218414_s_at	1S	5.02887e-04	200740_s_at	1S	5.02887e-04
218243_at	1S	5.02887e-04	200733_s_at	1S	5.02887e-04
218137_s_at	1S	5.02887e-04	200791_s_at	1S	5.02887e-04
218047_at	1S	5.02887e-04	1729_at	1S	5.02887e-04
218023_s_at	1S	5.02887e-04	200821_at	1S	5.02887e-04
216054_x_at	1S	5.02887e-04	200669_s_at	1S	5.02887e-04
204849_at	1S	5.02887e-04	200096_s_at	1S	5.02887e-04
203620_s_at	1S	5.02887e-04	200723_s_at	1S	5.02887e-04
203379_at	1S	5.02887e-04	201100_s_at	1S	5.02887e-04
203574_at	1S	5.02887e-04	201684_s_at	1S	5.02887e-04
204613_at	1S	5.02887e-04	201916_s_at	1S	5.02887e-04
203778_at	1S	5.02887e-04	200929_at	1S	5.02887e-04
203827_at	1S	5.02887e-04	201196_s_at	1S	5.02887e-04
203291_at	1S	5.02887e-04	200996_at	1S	5.02887e-04
204689_at	1S	5.02887e-04	201317_s_at	1S	5.02887e-04
203497_at	1S	5.02887e-04	201975_at	1S	5.02887e-04
204160_s_at	1S	5.02887e-04	201273_s_at	1S	5.02887e-04
203800_s_at	1S	5.02887e-04	201472_at	1S	5.02887e-04
221214_s_at	1S	5.02887e-04	201940_at	1S	5.02887e-04
220865_s_at	1S	5.02887e-04	201425_at	1S	5.02887e-04
221820_s_at	1S	5.02887e-04	201453_x_at	1S	5.02887e-04
210878_s_at	1S	5.02887e-04	201500_s_at	1S	5.02887e-04
211703_s_at	1S	5.02887e-04	201223_s_at	1S	5.02887e-04
209682_at	1S	5.02887e-04	201941_at	1S	5.02887e-04
209467_s_at	1S	5.02887e-04	200975_at	1S	5.02887e-04
210296_s_at	1S	5.02887e-04	201589_at	1S	5.02887e-04
211058_x_at	1S	5.02887e-04	207072_at	1S	5.05e-04
210213_s_at	1S	5.02887e-04	212896_at	1S	5.07e-04
211085_s_at	1S	5.02887e-04	220138_at	1S	5.07186e-04
212124_at	1S	5.02887e-04	221449_s_at	1S	5.07186e-04
212063_at	1S	5.02887e-04	202852_s_at	1S	5.07186e-04
210793_s_at	1S	5.02887e-04	207121_s_at	1S	5.07186e-04
202529_at	1S	5.02887e-04	238462_at	1S	5.08e-04
203138_at	1S	5.02887e-04	201068_s_at	1S	5.09e-04
203206_at	1S	5.02887e-04	219112_at	1S	5.15e-04
202128_at	1S	5.02887e-04	200629_at	1S	5.17e-04

200828_s_at	1S	5.21e-04	219812_at	1S	6.67609e-04
211495_x_at	1S	5.22e-04	213666_at	1S	6.67609e-04
202060_at	1S	5.24e-04	213956_at	1S	6.67609e-04
200818_at	1S	5.28e-04	212961_x_at	1S	6.67609e-04
203691_at	1S	5.34e-04	214305_s_at	1S	6.67609e-04
201384_s_at	1S	5.37e-04	214366_s_at	1S	6.67609e-04
221873_at	1S	5.39e-04	214055_x_at	1S	6.67609e-04
202836_s_at	1S	5.43e-04	217729_s_at	1S	6.67609e-04
212371_at	1S	5.5e-04	215739_s_at	1S	6.67609e-04
200630_x_at	1S	5.5e-04	203713_s_at	1S	6.67609e-04
209500_x_at	1S	5.51e-04	204771_s_at	1S	6.67609e-04
217836_s_at	1S	5.53e-04	203506_s_at	1S	6.67609e-04
201360_at	1S	5.53e-04	221507_at	1S	6.67609e-04
200035_at	1S	5.54e-04	212229_s_at	1S	6.67609e-04
213366_x_at	1S	5.56e-04	211948_x_at	1S	6.67609e-04
209296_at	1S	5.57e-04	205936_s_at	1S	6.67609e-04
201600_at	1S	5.59e-04	205297_s_at	1S	6.67609e-04
218661_at	1S	5.6356e-04	206829_x_at	1S	6.67609e-04
218508_at	1S	5.6356e-04	204890_s_at	1S	6.67609e-04
214496_x_at	1S	5.6356e-04	206335_at	1S	6.67609e-04
209610_s_at	1S	5.6356e-04	209333_at	1S	6.67609e-04
210154_at	1S	5.6356e-04	209088_s_at	1S	6.67609e-04
206937_at	1S	5.6356e-04	201234_at	1S	6.67609e-04
207627_s_at	1S	5.6356e-04	201602_s_at	1S	6.67609e-04
202286_s_at	1S	5.66964e-04	201369_s_at	1S	6.67609e-04
206697_s_at	1S	5.66964e-04	213341_at	1S	6.69e-04
204038_s_at	1S	5.71e-04	221443_x_at	1S	6.71e-04
208791_at	1S	5.76e-04	212100_s_at	1S	6.71e-04
218249_at	1S	5.83e-04	218134_s_at	1S	6.74e-04
207821_s_at	1S	5.86e-04	206698_at	1S	6.76645e-04
201358_s_at	1S	5.89e-04	200998_s_at	1S	6.77e-04
221804_s_at	1S	5.92e-04	215038_s_at	1S	6.78e-04
203888_at	1S	5.95878e-04	220731_s_at	1S	6.79e-04
203507_at	1S	5.95878e-04	216100_s_at	1S	6.79422e-04
202484_s_at	1S	5.96e-04	210775_x_at	1S	6.79422e-04
60471_at	1S	6.0e-04	202480_s_at	1S	6.79422e-04
214895_s_at	1S	6.0e-04	202374_s_at	1S	6.79422e-04
201498_at	1S	6.02e-04	205996_s_at	1S	6.79422e-04
203323_at	1S	6.11e-04	201264_at	1S	6.79422e-04
222682_s_at	1S	6.11e-04	201703_s_at	1S	6.79422e-04
219732_at	1S	6.16e-04	217763_s_at	1S	6.83e-04
213399_x_at	1S	6.16e-04	210667_s_at	1S	6.93442e-04
233559_s_at	1S	6.18e-04	209653_at	1S	6.93442e-04
201908_at	1S	6.21e-04	207085_x_at	1S	6.93442e-04
208263_at	1S	6.26e-04	57516_at	1S	6.95e-04
200701_at	1S	6.3e-04	209949_at	1S	7.01e-04
222065_s_at	1S	6.31e-04	201471_s_at	1S	7.04e-04
217717_s_at	1S	6.35e-04	202141_s_at	1S	7.07e-04
201563_at	1S	6.35e-04	208627_s_at	1S	7.1e-04
206139_at	1S	6.37e-04	206028_s_at	1S	7.10327e-04
203405_at	1S	6.39e-04	207117_at	1S	7.10327e-04
217839_at	1S	6.41619e-04	235816_s_at	1S	7.11e-04
202995_s_at	1S	6.41619e-04	208313_s_at	1S	7.11e-04
201590_x_at	1S	6.43e-04	201534_s_at	1S	7.19e-04
220288_at	1S	6.45e-04	217742_s_at	1S	7.21e-04
203244_at	1S	6.48e-04	212199_at	1S	7.22e-04
207466_at	1S	6.5e-04	221666_s_at	1S	7.24e-04
202038_at	1S	6.55e-04	203234_at	1S	7.31013e-04
212430_at	1S	6.57e-04	208490_x_at	1S	7.31013e-04
202077_at	1S	6.57e-04	200748_s_at	1S	7.33e-04
213491_x_at	1S	6.63e-04	201899_s_at	1S	7.36e-04
219717_at	1S	6.67609e-04	212616_at	1S	7.44e-04
219158_s_at	1S	6.67609e-04	217212_s_at	1S	7.44434e-04
219228_at	1S	6.67609e-04	206075_s_at	1S	7.44434e-04

220948_s_at	1S	7.5e-04	210283_x_at	1S	7.57566e-04
205812_s_at	1S	7.51e-04	212208_at	1S	7.57566e-04
202401_s_at	1S	7.56876e-04	211763_s_at	1S	7.57566e-04
40149_at	1S	7.57566e-04	210386_s_at	1S	7.57566e-04
35254_at	1S	7.57566e-04	202925_s_at	1S	7.57566e-04
46323_at	1S	7.57566e-04	202611_s_at	1S	7.57566e-04
32032_at	1S	7.57566e-04	202362_at	1S	7.57566e-04
64486_at	1S	7.57566e-04	203107_x_at	1S	7.57566e-04
59644_at	1S	7.57566e-04	202941_at	1S	7.57566e-04
219426_at	1S	7.57566e-04	202247_s_at	1S	7.57566e-04
218534_s_at	1S	7.57566e-04	202393_s_at	1S	7.57566e-04
219549_s_at	1S	7.57566e-04	202641_at	1S	7.57566e-04
218761_at	1S	7.57566e-04	202443_x_at	1S	7.57566e-04
218846_at	1S	7.57566e-04	202687_s_at	1S	7.57566e-04
219797_at	1S	7.57566e-04	202457_s_at	1S	7.57566e-04
212590_at	1S	7.57566e-04	202446_s_at	1S	7.57566e-04
213741_s_at	1S	7.57566e-04	202160_at	1S	7.57566e-04
214919_s_at	1S	7.57566e-04	202215_s_at	1S	7.57566e-04
214440_at	1S	7.57566e-04	202543_s_at	1S	7.57566e-04
212752_at	1S	7.57566e-04	202654_x_at	1S	7.57566e-04
214511_x_at	1S	7.57566e-04	202767_at	1S	7.57566e-04
212895_s_at	1S	7.57566e-04	202239_at	1S	7.57566e-04
212666_at	1S	7.57566e-04	202649_x_at	1S	7.57566e-04
212802_s_at	1S	7.57566e-04	205255_x_at	1S	7.57566e-04
212549_at	1S	7.57566e-04	206790_s_at	1S	7.57566e-04
212899_at	1S	7.57566e-04	206240_s_at	1S	7.57566e-04
213414_s_at	1S	7.57566e-04	205013_s_at	1S	7.57566e-04
218262_at	1S	7.57566e-04	205263_at	1S	7.57566e-04
218008_at	1S	7.57566e-04	205504_at	1S	7.57566e-04
217788_s_at	1S	7.57566e-04	205590_at	1S	7.57566e-04
217826_s_at	1S	7.57566e-04	207347_at	1S	7.57566e-04
217939_s_at	1S	7.57566e-04	208982_at	1S	7.57566e-04
217990_at	1S	7.57566e-04	208066_s_at	1S	7.57566e-04
218291_at	1S	7.57566e-04	208438_s_at	1S	7.57566e-04
218093_s_at	1S	7.57566e-04	209185_s_at	1S	7.57566e-04
217907_at	1S	7.57566e-04	208527_x_at	1S	7.57566e-04
218124_at	1S	7.57566e-04	208994_s_at	1S	7.57566e-04
217905_at	1S	7.57566e-04	208946_s_at	1S	7.57566e-04
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215633_x_at	1S	5.849246e-03	200989_at	1S	5.852224e-03
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219357_at	1S	7.557581e-03
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212926_at	1S	8.035721e-03
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209392_at	1S	8.237354e-03	35150_at	1S	9.214658e-03
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212862_at	1S	8.243436e-03	203611_at	1S	9.271398e-03
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221891_x_at	1S	8.443094e-03	212356_at	1S	9.450352e-03
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218870_at	1S	8.458772e-03	221196_x_at	1S	9.450352e-03
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203003_at	1S	8.531004e-03	202957_at	1S	9.481811e-03
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1552889_a_at	1S	8.548159e-03	226239_at	1S	9.539796e-03
202232_s_at	1S	8.588854e-03	227986_at	1S	9.555175e-03
202600_s_at	1S	8.596455e-03	208901_s_at	1S	9.614888e-03
208692_at	1S	8.634299e-03	217398_x_at	1S	9.640495e-03
200714_x_at	1S	8.653621e-03	212570_at	1S	9.652107e-03
220957_at	1S	8.654135e-03	210285_x_at	1S	9.655536e-03
201676_x_at	1S	8.660696e-03	204774_at	1S	9.666692e-03
220755_s_at	1S	8.669976e-03	225980_at	1S	9.675351e-03
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216388_s_at	1S	8.840424e-03	216902_s_at	1S	9.715506e-03
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203196_at	1S	8.840424e-03	220195_at	1S	9.761799e-03
202330_s_at	1S	8.840424e-03	209928_s_at	1S	9.843808e-03
209293_x_at	1S	8.840424e-03	213897_s_at	1S	9.898782e-03
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205849_s_at	1S	8.900462e-03	218301_at	1S	9.972049e-03
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